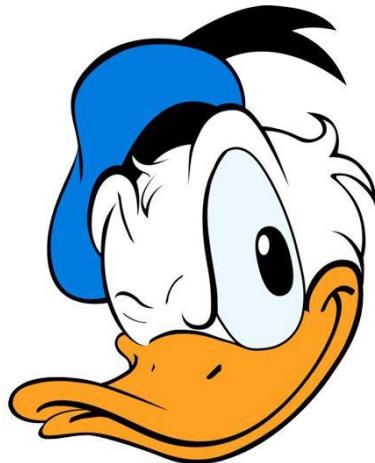
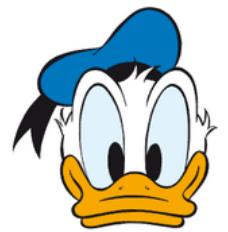


DERMATOLOGY

CME

2015





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Epstein–Barr virus: Dermatologic associations and implications

Part I. Mucocutaneous manifestations of Epstein–Barr virus and nonmalignant disorders

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Learning Objectives

After completing this learning activity, participants should be able to describe the basic science underlying the EBV virus, select the appropriate laboratory tests to evaluate for EBV, and identify the cutaneous manifestations of diseases associated with EBV.

Disclosures

None declared.

Epstein–Barr virus (EBV) is a ubiquitous virus that has been implicated in a wide range of human diseases, many of which have mucocutaneous manifestations. As a member of the herpesviridae family, EBV causes lifelong infection by establishing latency in B lymphocytes. An intact immune response is critical in preventing progression of EBV disease, and the clinical manifestations of infection are dependent on the intricate relationship between virus and host immune system. This review provides a comprehensive overview of the epidemiology, pathophysiology, and diagnostic testing in EBV infection. In part I of this continuing medical education article, the mucocutaneous manifestations of EBV infection are reviewed with an emphasis on pathophysiology and management. (J Am Acad Dermatol 2015;72:1-19.)

Key words: Epstein-Barr virus; human herpes virus 4; latency; infectious mononucleosis; papular acrodermatitis of childhood; oral hairy leukoplakia; hydroa vacciniforme; nonsexually related acute genital ulcers; histiocytic necrotizing lymphadenitis; lymphoproliferative; heterophile antibodies.

BACKGROUND

The Epstein-Barr virus (EBV), or human herpesvirus-4, is a member of the gamma-herpesviridae family, and is one of the most ubiquitous viruses known to humankind, infecting >90% to 95% of the world's adult population.^{1,2} The virus preferentially infects B lymphocytes and results in a wide spectrum of mucocutaneous and systemic diseases, ranging from self-limited illnesses to aggressive malignancies.

In 1964, EBV was discovered by electron microscopy of cells cultured from Burkitt lymphoma

tissue,³ making it the first identified human tumor virus. Four years later, it was shown to be the etiologic agent of heterophile-positive infectious mononucleosis (IM).¹ As medical technology advanced over the next several decades, EBV became the first human virus to have its genome fully sequenced.⁴ Humans are the only known host of EBV, but the virus is genetically related to viruses found in the oropharynx and B cells of Old World nonhuman primates, suggesting that it likely evolved from a nonhuman primate virus.⁵

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Abbreviations used:

CAEBV:	chronic active Epstein–Barr virus
CMV:	cytomegalovirus
EA:	early antigen
EBV:	Epstein–Barr virus
EBER:	Epstein–Barr virus–encoded RNA
EBNA:	Epstein–Barr virus nuclear antigen
GCS:	Gianotti–Crosti syndrome
HMB:	hypersensitivity to mosquito bites
HV:	hydroa vacciniforme
IM:	infectious mononucleosis
ISH:	in situ hybridization
KFD:	Kikuchi–Fujimoto disease
LC:	Langerhans cell
LCL:	lymphoblastoid cell line
LMP:	latent membrane protein
NRAGU:	non–sexually related acute genital ulcer
NF- κ B:	nuclear factor kappa light chain–enhancer of activated B cells
OHL:	oral hairy leukoplakia
PCR:	polymerase chain reaction
PTLD:	posttransplant lymphoproliferative disease
STAT1:	signal transducer and activator of transcription 1
VCA:	viral capsid antigen

EBV is an enveloped virus with an icosahedral nucleocapsid surrounding a double-stranded DNA genome of approximately 184-kb pairs in length, which encodes nearly 100 proteins.⁶ Two distinct types of EBV have been identified: types 1 and 2 (also called types A and B). They share 70% to 85% sequence homology, and result in lifelong infection with no identified type-specific differences in disease.⁶ In terms of geographic distribution, EBV-1 is prevalent worldwide, whereas EBV-2 is found more frequently in Africa. Dual infections of both types may occur, especially in immunosuppressed hosts.

EPIDEMIOLOGY

Key points

- Epstein–Barr virus is one of the most successful viruses identified, resulting in lifelong infection in >95% of the earth's adult population
- The clinical presentation of primary Epstein–Barr virus infection varies based on age at time of infection and socioeconomic factors

The prevalence of EBV infection increases with age, with >95% of the world's adult population being chronically infected.^{1,2} The age at initial infection varies based on geography and socioeconomic position. In developing countries and among socioeconomically disadvantaged populations, transmission occurs almost universally during infancy and early childhood.⁶ In developed countries, the prevalence approaches 60% to 80% in

children, and increases to 95% between 35 and 45 years of age.⁷

EBV is transmitted primarily through exposure to infected saliva, and IM is commonly referred to as the “kissing disease.” The virus is shed in oral secretions at high concentrations for >6 months after acute infection, followed by lifelong intermittent shedding at lower concentrations. Immunosuppression increases the probability of viral shedding in oral secretions.⁶ EBV has been reported in breast milk⁸ and male and female genital secretions,⁹ which can result in transmission by sexual contact.

Primary infection with EBV before 4 years of age tends to be asymptomatic or resemble a nonspecific viral illness.¹⁰ In contrast, primary infection in adolescents and adults results in the classic manifestations of IM in 30% to 50% of infected persons.¹¹ The incidence of IM in the United States is estimated at 20 to 70 per 100,000 persons annually.^{12,13} In developing countries and patients of lower socioeconomic status, symptomatic IM is rare because 80% to 100% of children become seropositive by 6 years of age.¹¹ The transfer of maternal antibodies confers passive immunity in infancy, resulting in a low incidence of primary EBV infections in the first year of life in developed countries. No seasonal changes in incidence have been identified, and there is no apparent sexual predominance.

PATHOPHYSIOLOGY

Key points

- Epstein–Barr virus has 2 life cycles within the body: a lytic cycle responsible for viral replication, and a latent cycle where the virus remains inactive within memory B cells until periods of reactivation
- In immunocompetent hosts, B lymphocytes infected with Epstein–Barr virus expressing a proliferative pattern of genes are rapidly removed by Epstein–Barr virus–specific T cell responses, resulting in a state of relatively harmless Epstein–Barr virus infection
- In immunocompromised hosts, Epstein–Barr virus is able to cause proliferation of lymphocytes, resulting in lymphoproliferative disease

Primary EBV infection

After inoculation within the oral cavity, EBV infects nasopharyngeal epithelial cells, followed by intracellular viral replication, cell lysis, and the release of virions that disseminate to contiguous structures, including the salivary glands and oropharyngeal lymphoid tissues.¹⁴ During an incubation period of 30 to 50 days, additional viral replication

results in viremia, with infection of B lymphocytes in the peripheral blood and dissemination throughout the lymphoreticular system.¹⁵

The primary cellular target of EBV is the B lymphocyte. The EBV envelope glycoprotein, gp350/220, binds to a B lymphocyte-specific surface molecule, CD21, inducing cell activation.^{16,17} EBV is also capable of infecting a variety of other cells, including T cells, natural killer (NK) cells, smooth muscle cells, endothelial cells, macrophages, and monocytes.^{5,7,14} The pathologic consequences of these infections are unclear, although EBV has been shown within smooth muscle cells of leiomyosarcomas that developed in immunocompromised patients.¹⁸

Primary EBV infection activates the innate and adaptive immune systems.¹⁹ EBV interacts with different cell types that are crucial mediators of innate immune responses, including NK cells, neutrophils, and monocytes/macrophages.²⁰ EBV macromolecules are detected by Toll-like receptor (TLR) 2 and TLR3 on human monocytes, lymphocytes, and keratinocytes, leading to downstream antiviral effects,^{21,22} and the EBV latent membrane protein-1 acts as a negative regulator of TLR9.²³

The adaptive immune response to EBV is characterized by both cellular and humoral responses. The cellular response includes activation of NK cells and T lymphocytes, with a predominant increase in the number of cytotoxic CD8⁺ lymphocytes.¹⁹ These cytotoxic T cells target lytic and latent EBV antigens and represent the major determinants in the control of acute EBV infection.^{24,25}

The humoral response produces antibodies directed against EBV lytic cycle and latent proteins, including EBNA1 and 2. Neutralizing antibodies are also produced against gp350.²⁶ These humoral responses play an important role in controlling the spread of the virus in the late phases of infection. Through the coordinated activation of innate and adaptive immunity, the circulating EBV burden in the peripheral blood is reduced to <1 copy/10⁵ circulating B lymphocytes.⁶ It has been estimated that about 1 in 10,000 to 100,000 memory cells contain EBV DNA in episomal form,²⁷ where EBV infection is maintained until reactivation.

EBV latency

Like all other herpesviruses, EBV establishes lifelong latency in the host upon resolution of the primary infection. Although EBV is capable of transforming B lymphocytes into continuously proliferating lymphoblasts in vitro,^{28,29} EBV persists as a harmless carrier state in the memory B cells of

immunocompetent hosts.^{7,29} Throughout the latency period, a percentage of the EBV-infected cells, most of which are epithelial cells,³⁰ will enter the lytic cycle and shed mature virions through secretions and systemically infect other B lymphocytes.

The EBV genome has a unique ability to produce a large number of different viral proteins, and the expression of different combinations of these proteins determines the form of infection. In lytic infection, EBV expresses the full complement of lytic cycle proteins and is capable of replicating within the host cell. In latent infection, the virus expresses only a small number of EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs). Four types of latency have been identified based on the expression patterns of the EBNAs and LMPs in lymphoblastoid cell lines (LCLs) in vitro^{31,32} (Table I).

Type 0 latency is characterized by complete silencing of the viral genome, and this expression profile is seen in long-lived memory cells of immunocompetent patients after resolution of IM. This is considered to be a state of "true latency" within the memory B cell reservoir.

Type I latency is a nonproliferative phenotype characterized by the expression of LMP2A either alone or together with EBNA1.³³ The expression of these viral proteins is crucial for establishing and maintaining EBV persistence in memory B cells of healthy individuals. EBNA1 is responsible for the persistence of latent EBV genomes as circular episomes in the B cell nucleus.³⁴ Through these episomes, viral genetic material remains separate from the host chromosomes, but is able to migrate to daughter B cells during mitosis. More recently, EBNA1 has been shown to alter key cellular proteins and pathways, including p53,³⁵ promyelocytic leukemia nuclear bodies,³⁶ nuclear factor kappa light chain-enhancer of activated B cells (NF- κ B),³⁷ and signal transducer and activator of transcription 1.³⁸ Lymphocytes with a type I latency program have been reported in Burkitt lymphoma and gastric carcinoma.^{27,39,40}

Type II latency cells exhibit expression of EBNA1 and varying levels of other latent proteins, but lack expression of 1 of the 2 pivotal proteins required for transformation, LMP1 or EBNA2. Type II latency can be further classified into types IIa (expression of LMP1, but not EBNA2) or IIb (expression of EBNA2, but not LMP1). Cells with this expression profile have been identified in IM, Hodgkin lymphoma, nasopharyngeal carcinoma, and NK/T-cell lymphoma.^{27,39,40}

Type III latency is characterized by the expression of all 9 latency proteins, and has been designated the "growth program" because of its ability to generate

Table I. Types of Epstein–Barr virus latency and associated conditions

Latency type*	Antigens expressed	Infected normal B cells	Associated conditions
0	EBERs 1 and 2	Memory B cells	Healthy carrier
I	EBNA1 LMP2a	Dividing memory cells	Burkitt lymphoma, AIDS-related diffuse large B cell lymphoma, Monomorphic PTLD, primary effusion lymphoma, and gastric carcinoma
II	EBNA1	Germinal center cells	Classic Hodgkin lymphoma, natural killer/T cell lymphoma, and nasopharyngeal carcinoma
III ("growth program")	EBNAs 1-6 LMP1 LMP2a LMP2b	Naïve cells	EBV-associated PTLD, AIDS-related immunoblastic lymphoma, and chronic active EBV infection

EBER, Epstein–Barr virus–encoded RNA; EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; LMP, latent membrane protein; PTLD, posttransplant lymphoproliferative disorder.

*Epstein–Barr virus–encoded RNAs are expressed in all Epstein–Barr virus latency programs.

autonomous proliferating LCLs in vitro.³² The viral proteins expressed in this latency program are highly immunogenic; therefore, in immunocompetent individuals, lymphocytes expressing a type III latency profile are present only during the acute phase of primary EBV infection before being eliminated by EBV-specific T cell responses. However, patients with impaired immune function are unable to develop strong EBV-specific T cell responses, and are at high risk for the development of EBV-positive lymphoproliferative disease.¹⁶ Cells with this latency program have been identified in posttransplant lymphoproliferative disease (PTLD), AIDS-related immunoblastic lymphoma, and chronic active EBV infection.^{27,40,41}

Chronic active EBV infection

Most primary EBV infections resolve spontaneously, but in some cases EBV can cause chronic infections in immunocompetent hosts. Chronic active EBV (CAEBV) infection is defined as a persistent EBV infection with an unusual pattern of EBV-related antibodies and high viral loads in the peripheral blood.⁴² The antibody profile is characterized by elevated immunoglobulin G (IgG)—viral capsid antigen (VCA) titers with positive anti-EBNA and negative IgM-VCA antibodies. It has been reported predominantly in Asian children, suggesting the possibility of distinct viral strains prevalent in this region or a genetic predisposition to CAEBV infection. It has been considered by some to be a systemic EBV⁺ lymphoproliferative disease.⁴³

CAEBV infection is characterized by chronic or recurrent IM-like symptoms, and is associated with life-threatening complications, including virus associated hemophagocytic syndrome, interstitial pneumonia, lymphoma, coronary artery aneurysms,

and central nervous system involvement. The clonal expansion of EBV-infected T cells and NK cells appears to play a central role in the pathogenesis of CAEBV infection.⁴⁴ Hypersensitivity to mosquito bites and severe hydroa vacciniforme (HV)—like eruptions have also been associated with CAEBV.

DIAGNOSTIC TESTING

Key points

- For suspected primary Epstein–Barr virus infection, a heterophile antibody test should be performed, followed by Epstein–Barr virus serology when the heterophile test is negative but clinical suspicion remains high
- Epstein–Barr virus–encoded RNA in situ hybridization is considered the gold standard for detecting and localizing latent Epstein–Barr virus in tissue samples

Laboratory findings

Mild thrombocytopenia and mild to moderate elevation of transaminases are seen in up to 50% of uncomplicated cases of IM.⁴⁵ Mild leukocytosis ($10\text{--}20 \times 10^3/\mu\text{L}$) is common, with atypical lymphocytes accounting for 20% to 40% of the total white blood cells on peripheral smear.⁶ Atypical lymphocytes represent activated CD8⁺ suppressor/cytotoxic T cells in response to EBV-infected B cells. Atypical lymphocytes are not specific to EBV infection, and may also be seen in drug reactions,⁴⁶ acquired cytomegalovirus (CMV) infection,⁴⁶ toxoplasmosis,⁴⁷ viral hepatitis, rubella, roseola,⁴⁸ mumps, tuberculosis, typhoid, Mycoplasma infection, and malaria.

Heterophile antibody

Heterophile antibodies are defined by the ability to agglutinate cells from the serum of a different

Table II. Diagnostic testing for Epstein–Barr virus infection

Clinical status	Serologic response to EBV			
	Heterophile antibodies	IgM-VCA	IgG-VCA	EBNA IgG
Susceptible	—	—	—	—
Acute primary infection	+	+	+/-	—
Previous infection	—	—	+	+

Early antigen titers may be positive in primary or previous EBV infection.

EBNA, Epstein–Barr virus nuclear antigen; EBV, Epstein–Barr virus; Ig, immunoglobulin; VCA, viral capsid antigen.

species.⁴⁹ Heterophile antibody titers >1:40 are considered positive for IM. The most widely used method for detecting heterophile antibodies is the qualitative rapid slide test, which uses horse red blood cells to achieve greater sensitivity.⁵⁰ The commercially available Monospot test (Meridian Bioscience, Cincinnati, OH), a latex agglutination assay, has a reported sensitivity of 85% and specificity approaching 100%.⁵¹

Despite a high sensitivity and specificity, the heterophile antibody tests have several limitations. The test has a significant false-negative rate during the first week of infection, and is of limited use in children <4 years of age.⁵² False-positive results have been reported in toxoplasmosis, babesiosis, malaria, rubella, primary HIV infection, and certain malignancies, particularly leukemias and lymphomas.^{53–55} Up to 10% of patients with IM are heterophile-negative; therefore, if the heterophile test result is negative and EBV infection is suspected clinically, serologic testing should be performed.

Serology

Specific antibody testing is more time-consuming and expensive, but is especially useful in cases of heterophile-negative EBV. Titers of 3 different antibodies are required to determine the state of EBV infection: VCA, EBNA, and early antigen (EA)^{56,57} (Table II).

Acute EBV infection is uniformly characterized by a rapid IgM and IgG antibody response to VCA. Anti-VCA IgM is the single most valuable and specific serologic test in confirming primary EBV infection. They appear before the onset of symptoms and remain positive for up to 3 months. Rheumatoid factor has been reported to cause a false-positive IgM-VCA.⁵⁸ IgG-VCA peaks later in the acute phase, declines over several weeks to months, and then remains positive for life. IgA-VCA antibodies titers are significantly increased in patients with nasopharyngeal carcinoma.

Antibodies to EBNA gradually appear 3 to 4 months after initial infection and remain positive for life. The presence of EBNA antibodies without IgM-VCA indicates a past persistent infection, whereas the absence EBNA antibodies with positive IgM-VCA indicates recent infection within a few weeks to months. Antibodies to EA are detectable in 80% of patients during the acute phase of IM, persist for several months, and may remain intermittently positive at low titers for many years. Very high titers of EA antibodies may be seen in patients with Burkitt lymphoma, nasopharyngeal carcinoma, or immunocompromised patients.

Similar to the heterophile antibody test, EBV serologies may be falsely negative early in the course of infection, and in children <2 years of age.⁵⁹ Titers are also more difficult to interpret in immunocompromised patients because of variable antibody responses.⁶⁰ False-positive results for IgM-VCA have been reported during the course of other infections, including CMV, Toxoplasma, parvovirus B19, hepatitis A, and HIV.^{61–70}

Other tests

Viral culture of EBV is difficult and usually performed only for research purposes. Real-time polymerase chain reaction (PCR) assays appear to be sensitive⁷¹ and useful for defining infection status, especially in immunocompromised patients and those at risk of developing EBV-related disorders.⁷² It has been suggested that EBV PCR could lead to at least a 16% increase in the number of positive diagnoses of primary EBV infection compared with standard serologies.⁷³ Serial EBV viral loads using PCR have been used to monitor response to treatment in patients with PTLD.⁷⁴ Unfortunately, PCR lacks the ability to localize the expression of EBV within specific cells.

EBV-encoded RNA (EBER) in situ hybridization (ISH) identifies EBV transcripts or DNA in specific cell types within histologic lesions, and is considered the gold standard for detecting and localizing latent EBV in tissue samples.^{75–79} ISH is used diagnostically in several clinical situations, including confirmation of EBV-driven PTLD,⁸⁰ nasopharyngeal carcinoma, and EBV-related Hodgkin disease.

Immunohistochemistry of latent and lytic viral proteins also permits localization of EBV in histopathologic sections. Immunostains are available against EBNA1, EBNA2, LMP1, LMP2, BHRF1 (an EBV-encoded protein demonstrating functional homology to the human bcl-2 proto-oncogene product), BZLF1 (a transcriptional activator), and BMRF1 (a protein required for viral polymerase processivity).⁸¹ These are cost-effective and localize

EBV within histologic sections, but suffer from a lower sensitivity than EBER ISH.^{82,83}

EPSTEIN–BARR VIRUS–ASSOCIATED MUCOCUTANEOUS DISEASES

Key points

- **Mucocutaneous involvement is relatively uncommon in infectious mononucleosis, and is characterized by a constellation of relatively nonspecific findings**
- **“Ampicillin rash” is a distinct cutaneous eruption of unclear etiology that occurs in infectious mononucleosis patients within 1 week of beginning therapy with a number of antibiotic medications**

Infectious mononucleosis

As discussed above, primary EBV infection occurring before 4 years of age tends to be asymptomatic or resemble a nonspecific viral illness.¹⁰ In contrast, primary EBV infection in older patients produces the clinical syndrome of IM in 30% to 50% of infected persons.¹¹ The incubation period of EBV in adolescents and adults lasts approximately 30 to 50 days, at which time the characteristic triad of fever ($\leq 40^{\circ}\text{C}$), pharyngitis, and lymphadenopathy is seen. Common accompanying symptoms include malaise, fatigue, shaking chills, and headache. Evidence suggests that the acute CD4 $^{+}$ and CD8 $^{+}$ T cell response likely contributes to the symptoms of IM.⁸⁴

Physical examination typically reveals non-exudative pharyngitis, with or without tonsillar enlargement. When exudates are present, the pharyngitis of IM is nearly indistinguishable from that of group A Streptococcus. Approximately 30% of IM patients have concomitant group A streptococcal carriage in the oropharynx, further complicating the diagnosis. Lymphadenopathy of the cervical and submandibular lymph nodes is most common, with the axillary and inguinal lymph nodes occasionally involved. Epitrochlear lymphadenopathy is a fairly specific but not sensitive finding of IM. Splenomegaly develops within the first 3 weeks of illness in approximately 15 to 65% of cases, and splenic rupture is a rare complication in 0.1% to 0.2% of cases.^{85,86} Hepatomegaly and jaundice are less common, being reported in up to 10% of cases.

Mucocutaneous involvement occurs after the incubation period of 30 to 50 days in 3% to 15% of patients.¹⁵ The most common presentation is a morbilliform eruption on the trunk and upper extremities, which may spread to involve the face and forearms, typically lasting up to 7 days. It may be

difficult to distinguish from drug hypersensitivity reactions, cutaneous lymphoma, and other infectious eruptions, including primary CMV infection, human herpesvirus-6, rubella, group A streptococcal infection, and primary HIV infection. Less common presentations include urticarial, petechial, purpuric, erythema multiforme-like, and herpetiform eruptions.^{86,87}

Other findings include pinhead-sized petechiae at the junction of the soft and hard palate seen in approximately 25% of cases, and usually occurring between days 5 and 17 of illness. Similar palatal petechiae can be seen in rubella (Forscherheimer spots), roseola, viral hemorrhagic fevers, group A Streptococcus infection, and thrombocytopenia. The Hoagland sign (bilateral upper eyelid edema) may be present in up to 50% of patients, but is less helpful diagnostically because it presents only during the first few days of illness.^{87,88} Other rare cutaneous associations with IM include transient cold urticaria,⁸⁹ purpura caused by immune-related thrombocytopenia,⁹⁰ and erythema nodosum.⁹¹ Most recently, cutaneous lymphoid hyperplasia presenting as a pedunculated papule on the tongue was described as a presenting sign of IM.⁹²

“Ampicillin rash” was first reported in the 1960s as a maculopapular eruption unique to patients with IM treated with ampicillin. Since that time, a similar eruption has been reported with a number of antibiotics, including amoxicillin, methicillin, erythromycin, levofloxacin, tetracyclines, and cephalexin. The incidence has been estimated at being between 80% and 100%, but a recent study suggests that the true incidence is significantly lower.⁹³ A generalized, pruritic eruption of erythematous to copper-colored macules usually develops 7 to 10 days after administration of the antibiotic (Fig 1). The eruption lasts approximately 1 week, and usually requires only symptomatic treatment and discontinuation of the offending antibiotic. The pathogenesis of this eruption is not known, but has been suggested to represent an allergic reaction,⁹⁴⁻⁹⁶ a transient immunostimulation by EBV, or the result of a complex formed between antibiotic and polyclonal antibody.⁹⁷ Several investigators have shown that ampicillin can be readministered after resolution of IM without any adverse effect, arguing against an allergic etiology.^{96,98}

The mainstay of treatment for IM is symptomatic, including adequate hydration, analgesics, antipyretics, and rest. Acyclovir was shown to decrease oropharyngeal shedding of EBV, but provided no significant clinical benefit.⁹⁹ Systemic corticosteroids are recommended in patients with significant



Fig 1. Amoxicillin rash of infectious mononucleosis. Note the diffuse pink to erythematous macules and papules on the lower extremities. (Photograph courtesy of James Treat, MD.)

pharyngeal edema that threatens respiratory compromise. Most clinical and laboratory findings resolve within 2 to 4 weeks after diagnosis, although cervical lymphadenopathy and fatigue may persist for up to 6 months.^{100,101} Most patients resume usual activities within 2 to 3 months.¹⁰⁰

NON-SEXUALLY RELATED ACUTE GENITAL ULCERS (LIPSCHÜTZ ULCERS)

Key points

- Non-sexually related acute genital ulcers are painful ulcers, most commonly located on the labia minora, occurring in prepubertal and adolescent female patients
- These ulcers may be misdiagnosed as sexually transmitted diseases or mistaken for signs of sexual abuse in children, causing significant physical and emotional distress for the patient and parents
- The most common cause of non-sexually related acute genital ulcers is primary Epstein-Barr virus infection, but a variety of other infectious etiologies have been reported

Non-sexually related acute genital ulcers (NRAGUs) are painful ulcerations of the external genitalia occurring primarily in adolescent females, with a mean age of onset of 14.5 years.¹⁰² They are often misdiagnosed as herpes simplex virus infection or Behçet disease, and may prompt an evaluation for

sexual abuse, causing significant physical and emotional distress for the patient and parents.¹⁰³ An incidence of between 10% and 30% among adolescent women has been reported,^{104,105} but this is likely an underestimate. In the largest series to date, EBV was the most commonly identified infectious cause of NRAGUs.¹⁰⁴ Other infectious agents implicated include CMV,¹⁰⁶ *Mycoplasma pneumoniae*,¹⁰⁷ mumps,¹⁰⁸ group A Streptococcus, Salmonella, Toxoplasma, and influenza A virus.¹⁰⁹ Noninfectious etiologies include Crohn's and Behçet disease.¹¹⁰

Patients typically present with ≥ 1 very painful ulcers, with characteristic purple-red ragged edges, most commonly on the medial or outer surface of the labia minora. Less commonly, involvement of the labia majora and extension onto the proximal thighs has been reported.¹⁰⁴ Lymphadenopathy distant from the site of ulceration is common. Nonspecific prodromal symptoms, including fatigue, anorexia, headache, and low-grade fever, often precede the appearance of ulcers, and most patients will eventually develop the characteristic symptoms of IM. In 1 case series, 70% of cases had a history of oral aphthosis.¹¹¹ NRAGUs related to EBV usually occur as a solitary episode, a feature that distinguishes them from herpes and aphthosis, which tend to be recurrent.¹⁰⁴

The pathophysiology of these ulcerations remains unclear. It was initially thought that the ulcerations resulted from sexual transmission of the virus; however, most patients report no previous sexual contacts.¹¹² It is now believed that ulceration is a complication of EBV viremia during acute infection, which might reach the genital skin via lymphocytic infiltration, hematogenous circulation, viral shedding in the urine, or autoinoculation with saliva or cervicovaginal fluid.¹¹² Once EBV reaches the genital mucosa, it may result in ulceration by 1 of the following mechanisms: a cytotoxic immune response to the virus, immune complex deposition resulting in a type III hypersensitivity, or direct cytolysis caused by EBV replication in vulvar keratinocytes.^{104,112}

Histologically, there is vasculitis with a mixed cell infiltrate and overlying ulceration.^{102,113} Diagnosis relies on excluding other causes of genital ulceration and detecting EBV DNA by PCR on vulvar swabs or confirming acute EBV infection serologically.^{102,114} NRAGU is a self-limiting condition, usually resolving spontaneously within 2 to 6 weeks without scarring. Treatment is supportive and may include pain control, topical corticosteroids, and short courses of oral prednisone.

GIANOTTI–CROSTI SYNDROME (PAPULAR ACRODERMATITIS OF CHILDHOOD)

Key points

- Gianotti–Crosti syndrome is a benign, self-limited papular or papulovesicular eruption seen in young children that represents a response to viral infection
- Hepatitis B was the first identified viral etiology of Gianotti–Crosti syndrome, but with the increased frequency of immunization, Epstein–Barr virus is now the most common cause of this syndrome worldwide

Gianotti–Crosti syndrome (GCS), also known as papular acrodermatitis of childhood, is a self-limited childhood eruption that occurs, most commonly, in response to a viral infection. It has a worldwide distribution, and nearly all patients are between 3 months and 15 years of age, with a peak between 1 and 6 years of age.¹¹⁵ There is no racial predilection, but it is more common in spring and early summer, and may affect male children more frequently.

A viral cause was initially suspected by Gianotti, and was later confirmed with the identification of hepatitis B surface antigen (HBsAg) in the serum of affected children.^{116,117} With the increased use of anti-HBV immunization, EBV is now the most common cause of GCS worldwide.^{118,119} Less common infectious etiologies include hepatitis A virus, CMV, human herpesvirus-6, coxsackievirus, *Bartonella henselae*, *M pneumoniae*, and beta-hemolytic streptococci. GCS-like reactions have recently been reported as a result of cell-mediated immune responses against molluscum contagiosum.¹²⁰ Several immunizations have also been implicated, including diphtheria-tetanus, hepatitis A, B, and C, and influenza virus vaccines. The pathogenesis of GCS remains unclear, but it may represent a virus-induced delayed hypersensitivity reaction.¹²¹ Viral particles or antigens have not been detected in the skin lesions of GCS, suggesting that it does not involve a direct local interaction with viral antigens.¹²²

The disease usually begins abruptly with cutaneous lesions, although a prodrome of upper respiratory tract symptoms or diarrhea may precede the eruption by up to 1 week. The typical cutaneous lesions are monomorphic pink to red-brown papules or papulovesicles symmetrically distributed on the cheeks, extensor surfaces of the extremities, and buttocks (Fig 2). The lesions tend to be asymptomatic or slightly pruritic and may be accompanied by systemic findings, such as malaise, low-grade fever, or diarrhea. Lymphadenopathy is



Fig 2. Gianotti–Crosti syndrome. Note the monomorphic, erythematous papules and papulovesicles on the cheek of an infant. (Photograph courtesy of Dirk Elston, MD.)

seen in 25% to 35% of patients, and hepatosplenomegaly is uncommon. Histopathologic features are nonspecific, including acanthosis, spongiosis, a superficial and deep perivascular lymphocytic infiltrate, and focal parakeratosis. The eruption usually resolves spontaneously within 3 to 4 weeks, but may last up to 8 weeks. Treatment is supportive, typically with oral antihistamines or topical anti-pruritic medications.

HYPERSENSITIVITY TO MOSQUITO BITES

Key points

- Hypersensitivity to mosquito bites is characterized by intense local cutaneous reactions and systemic symptoms, and is seen primarily in children and adolescents in Asia and Central America
- It may be related to reactivation of Epstein–Barr virus–infected natural killer cells, and has been associated with chronic active Epstein–Barr virus infection and natural killer/T-cell leukemia/lymphoma

Hypersensitivity to mosquito bites (HMBs) is a disease associated with chronic EBV infection, and is characterized by intense local cutaneous reactions including erythema, bullae, necrosis, and ulceration.^{123,124} Systemic symptoms, including high-grade fever, malaise, lymphadenopathy, hepatosplenomegaly, hepatic dysfunction, hematuria, and proteinuria, often accompany the cutaneous reaction. Most cases have been reported from Japan, Taiwan, Korea, and Mexico. The majority of cases occur within the first 2 decades of life, with a median age at diagnosis of 6.7 years.¹²⁵ HMB can be distinguished from a simple allergic reaction to mosquito bites by the severity of the cutaneous reaction and associated systemic symptoms.



Fig 3. Exaggerated response to arthropod assault. Note the vesicles and hemorrhagic bullae on the lower extremity of a patient with chronic lymphocytic leukemia. (Photograph courtesy of Dirk Elston, MD.)

HMB has been reported to have a strong association with chronic EBV infection and NK/T-cell leukemia/lymphoma.¹²⁵ It has also been observed in non–EBV-related lymphoproliferative diseases, including chronic lymphocytic leukemia (Fig 3) and mantle cell lymphoma.^{126,127} Hodgkin lymphoma with EBV positivity has also been reported in a patient with HMB.¹²⁸ The etiology remains unclear, but it has been hypothesized that the mosquito salivary gland extract may trigger EBV reactivation in latently infected NK cells.^{129,130} Once reactivated, EBV oncogenes, such as LMP1, may induce immortalization of NK cells, eventually progressing to lymphoma. The reaction resolves spontaneously, usually healing with a scar. Treatment is symptomatic, and repeated episodes occur with future mosquito bites. Regular clinical follow-up of patients with HMB is recommended to assess for the development of lymphoproliferative disease.

ORAL HAIRY LEUKOPLAKIA

Key points

- **Oral hairy leukoplakia is a benign, Epstein–Barr virus–associated disease of the oral mucosa seen in immunocompromised individuals that must be distinguished from oral candidiasis**
- **In HIV-positive individuals, the presence of oral hairy leukoplakia indicates poor disease control, and predicts disease progression to AIDS**

Oral hairy leukoplakia (OHL) is a benign, EBV-associated disease of the oral mucosa seen in immunocompromised individuals. It was originally described in HIV-positive individuals by Greenspan et al¹³¹ in 1981 and remains one of the most common oral diseases in this population with a reported point prevalence of 25% to 53%.¹³² OHL is most frequently



Fig 4. Oral hairy leukoplakia. Typical presentation of firmly attached, corrugated white patches on the lateral borders of the tongue. (Photograph courtesy of Misha Rosenbach, MD.)

associated with HIV, but has been reported in other states of immunosuppression, including ulcerative colitis, pemphigus vulgaris, bullous pemphigoid, organ transplantation,¹³³ Behçet disease,¹³⁴ multiple myeloma,¹³⁵ leukemia,^{136,137} and in patients who are receiving chemotherapy. In HIV-positive patients, the risk of developing OHL increases with decreasing CD4⁺ cell count and increasing viral load,¹³⁸ and has prognostic value as an indicator of disease progression, with one-third of patients developing AIDS within 3 years.¹³⁹

OHL typically appears as unilateral or bilateral white to gray plaques on the lateral or dorsolateral aspect of the tongue (Fig 4). Other less common locations include the buccal mucosa, floor of the mouth, soft palate, and gingival and oropharyngeal mucosa. The plaques are firmly attached to the underlying mucosa, and only the superficial layers can be removed by scraping, a distinguishing feature from oral candidiasis. Irregular vertical folds and ridges result in a corrugated appearance, but less developed OHL lesions and those located on the ventral surface of the tongue frequently present as subtle flat white patches.¹⁴⁰ OHL is usually asymptomatic, but patients may report soreness, alteration of taste, or a burning sensation. Cosmetic concerns may result in significant psychological distress for the patient.

While the association of EBV with OHL has been clearly established, its exact role remains unclear. OHL may represent repeated direct infection of tongue epithelium from EBV in the saliva or reactivation of latent EBV infection within basal epithelial cells.^{141,142} EBV replication results in decreased mucosal Langerhans cells (LCs), which may allow for viral evasion of the adaptive immune response and continued infection.¹⁴³ Within infected mucosal epithelial cells, EBV upregulates the antiapoptotic molecule Bcl-2 in the superficial layers

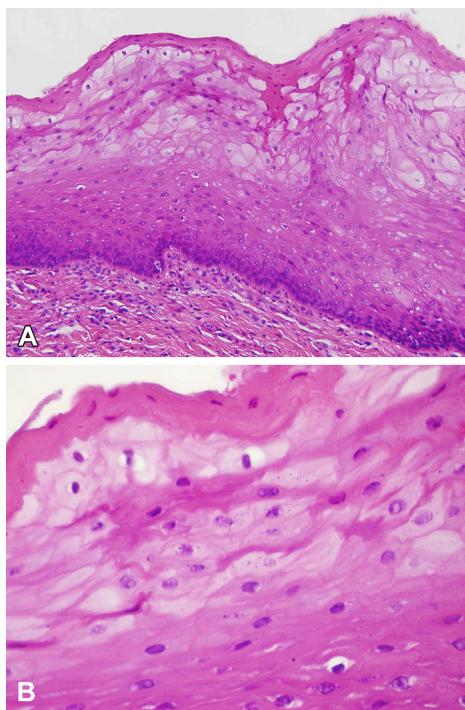


Fig 5. Oral hairy leukoplakia. **A**, Histopathologic features revealing epithelial acanthosis and parakeratosis, with a prominent band of pale, vacuolated cells in the upper layers of the oropharyngeal epithelium. **B**, Perinuclear halos and margination of condensed chromatin against the nuclear membrane.

of OHL lesions, resulting in the characteristic hyperkeratosis seen clinically.¹⁴⁴

The histopathologic features of OHL include hyperkeratosis with parakeratosis, acanthosis, and papillomatosis. A band of koilocyte-like pale, vacuolated cells is characteristically present within the stratum spinosum (Fig 5, A). Nuclear changes seen in the vacuolated cells include eosinophilic intranuclear inclusions (Cowdry Type A) and margination of condensed chromatin against the nuclear membrane¹⁴⁵ ("nuclear beading"; Fig 5, B). Candidal superinfection is present in approximately 80% of cases.¹⁴⁶ EBV can be demonstrated in lesional tissue using ISH, immunohistochemistry, PCR, and electron microscopy.

The differential diagnosis of OHL includes white sponge nevus, lichen planus, idiopathic leukoplakia, smoker's keratosis, and oral candidiasis. Unlike OHL, the plaque of oral candidiasis can be easily removed with a tongue blade, revealing an erythematous base. The histopathologic features of OHL overlap with those of idiopathic leukoplakia, making demonstration of EBV in lesional tissue essential to confirm the diagnosis. OHL is usually asymptomatic, may resolve spontaneously, and has no known

malignant potential.¹⁴⁷ Therefore, treatment is usually reserved for symptomatic cases or cosmetic concerns of the patient. Treatment options include systemic antiviral therapy,¹⁴⁸ topical podophyllin,¹⁴⁹ topical retinoids,¹⁵⁰ gentian violet,¹⁵¹ surgical excision, and cryotherapy.¹⁵² Regardless of the treatment modality, OHL often recurs after treatment cessation.

KIKUCHI–FUJIMOTO DISEASE (HISTIOCYTIC NECROTIZING LYMPHADENITIS)

Key points

- Kikuchi–Fujimoto disease is a benign, self-limited necrotizing lymphadenitis that most likely represents a hyperimmune reaction to an infectious agent, most likely Epstein–Barr virus
- There may be an association between Kikuchi–Fujimoto disease and systemic lupus erythematosus, and antinuclear antibody screening may be warranted

Kikuchi–Fujimoto disease (KFD), or histiocytic necrotizing lymphadenitis, is a benign, self-limited disease characterized by fever and painful lymphadenopathy.^{153,154} It affects all ethnic groups, although it may be more common in Asia, and occurs most often in women <40 years of age.¹⁵⁵

The most common clinical manifestation is cervical lymphadenopathy with or without fever. Other findings include fatigue, arthralgia, weight loss, arthritis, anorexia, chills, and splenomegaly. Nonspecific mucocutaneous findings are present in ≤ 40% of cases,¹⁵⁶ including cutaneous and oral ulcerations and erythematous macules, papules, or patches. The cutaneous histopathologic findings are variable, including a dermal lymphohistiocytic infiltrate, nonneutrophilic karyorrhexis, basal vacuolar change, and deposition of mucin.^{157–159} A definitive diagnosis is made by obtaining a lymph node biopsy specimen, which reveals characteristic paracortical zones of eosinophilic fibrinoid necrosis surrounded by a mixed infiltrate of foamy histiocytes and debris-laden macrophages.¹⁶⁰

The cause of KFD remains unknown, but clinical and pathologic features support a hyperimmune reaction to an infectious agent. The most commonly detected infectious agent in KFD is EBV.^{156,161–164} Other studies have revealed few or no EBV⁺ cells in lymph node biopsy specimens using PCR and EBER ISH, leading to a debate over a causative role for EBV in KFD.^{165–168} Other infectious etiologies have been proposed, including human herpesvirus-8,¹⁶⁹ HIV,¹⁷⁰ human

T-lymphotropic virus-1,¹⁷¹ dengue virus,¹⁷² parvovirus B19,¹⁷³ *Yersinia enterocolitica*,¹⁷⁴ Bartonella,¹⁷⁵ Brucella,¹⁷⁶ and Toxoplasma.¹⁷⁷

KFD resolves spontaneously in 1 to 4 months, and there is no reported association with hematologic malignancy. Treatment is primarily supportive, and nonsteroidal antiinflammatory drugs, corticosteroids, hydroxychloroquine, methotrexate, and intravenous immunoglobulin have been used in severe cases. Associations between systemic lupus erythematosus and KFD have been reported, and some authors recommend antinuclear antibody screening and clinical follow-up for evidence of autoimmune disease.^{178,179}

HYDROA VACCINIFORME

Key points

- Typical hydroa vacciniforme is an Epstein–Barr virus–associated scarring photosensitivity disorder of childhood with no associated risk of lymphoproliferative disease
- Severe hydroa vacciniforme–like eruptions have been classified as hydroa vacciniforme–like lymphoma according to the 2008 World Health Organization lymphoma classification
- Severe hydroa vacciniforme–like eruptions occur on sun-exposed and protected areas, do not resolve after adolescence, and are associated with systemic complications

HV is a rare childhood photosensitivity disorder of unknown pathogenesis. Previously, 2 forms have been recognized: typical HV and severe HV-like eruptions.¹⁸⁰ Severe, or atypical, HV-like eruptions are characterized by ulcerative cutaneous lesions on exposed and photoprotected areas, facial edema, fever, and systemic complications, such as liver damage and hematologic abnormalities. These atypical eruptions have been reclassified as HV-like lymphoma according to the 2008 World Health Organization lymphoma classification,¹⁸¹ and will be discussed further in part II of this continuing medical education article. Typical HV occurs mostly in young children and is characterized by recurrent vesiculopapules on sun-exposed areas. The erythematous vesiculopapules become umbilicated with central necrosis, later healing with small pox–like scars within 1 to 2 weeks. Involvement of the oral mucosa has also been reported.^{182,183} Mild burning, stinging, or pruritus is common within 6 hours of sun exposure, and mild conjunctivitis or keratitis is not uncommon.^{184,185} Rare features include photoonycholysis, earlobe mutilation, and partial absorption of bone.¹⁸⁶ The differential

Table III. Other mucocutaneous conditions possibly related to Epstein–Barr virus infection

Conditions	EBV shown in tissue
Erythema multiforme, ¹⁹⁹ erythema nodosum, ^{91,200,201} erythema annulare centrifugum, ^{202,203} granuloma annulare–like eruptions, ^{204–206} pityriasis lichenoides, ^{207–209} acute urticaria, ²¹⁰ cold urticaria, ^{89,211} chronic bullous disease of childhood/linear immunoglobulin A bullous dermatosis, ²¹² and DRESS syndrome ^{213,214}	No
Leukocytoclastic vasculitis ^{215–217}	Yes*

DRESS, Drug reaction with eosinophilia and systemic symptoms.

*Epstein–Barr virus genome has been detected by Epstein–Barr virus–encoded RNA in situ hybridization in some cases of large vessel vasculitis.

diagnosis includes erythropoietic protoporphyria, polymorphous light eruption, actinic prurigo, and porphyria cutanea tarda. HV can be distinguished from erythropoietic protoporphyria and porphyria cutanea tarda by testing for porphyrin levels. The histopathology of HV reveals intraepidermal vesication with reticular degeneration, progressing to confluent epidermal necrosis in later lesions.¹⁸⁷ A dense perivascular lymphohistiocytic infiltrate may be present in the dermis. Direct immunofluorescence is usually negative, but may rarely show scattered granular deposits of C3 at the dermoepidermal junction.¹⁸⁷ Systemic symptoms are generally absent, and the disease tends to resolve spontaneously by early adult life. There is no specific epidemiologic distribution, but most patients have been reported in the United States, United Kingdom, Japan, and Europe.

The pathophysiology of typical HV remains unclear, but the identification of EBV⁺ T lymphocytes by EBER in cases of HV strongly supports an association with EBV infection.¹⁸⁸ Latent EBV infection has been detected in HV and HV-like lymphoma,^{189–192} with higher EBV DNA loads reported in HV-like lymphoma.¹⁸⁰ Hirai et al¹⁹³ recently showed that increased numbers of EBV⁺ gamma/delta T cells are present in the peripheral blood of HV and HV-like lymphoma patients.

Treatment of typical HV consists of strict photoprotection with broad-spectrum sunscreens that block the ultraviolet A light range. Low-dose prophylactic narrowband ultraviolet B light phototherapy during the spring months may reduce disease severity.¹⁹⁴ Oral antimalarial drugs,

Table IV. Epstein–Barr virus–associated mucocutaneous diseases

Disease	Demonstration of EBV in tissue	Epidemiology	Other possible etiologies	Cutaneous findings	Differential diagnosis	Associations/risks
Infectious mononucleosis	Yes	Worldwide	None	Morbilliform eruption on trunk and extremities; palatal petechiae; bilateral upper eyelid edema	Drug hypersensitivity reaction, infectious morbilliform eruptions (ie, CMV, HHV-6, rubella, and group A Streptococcus), acute viral hepatitis, and primary HIV infection	Rarely splenic rupture; “ampicillin rash” in 30–100%
Non–sexually related acute genital ulcers	No	Worldwide; prepubertal and adolescent girls	CMV, <i>Mycoplasma pneumoniae</i> , group A Streptococcus, influenza A virus, mumps, <i>Salmonella</i> , and <i>Toxoplasma</i>	Painful ulcers with purple-red ragged borders most commonly on labia minora; distant lymphadenopathy	Sexually transmitted diseases (ie, HSV, syphilis, chancroid), Crohn’s disease, and Behcet disease	None
Gianotti–Crosti syndrome	No	Worldwide	Viral infections (ie, hepatitis B virus, hepatitis A virus, CMV, HHV-6, and coxsackievirus); bacterial infections (ie, <i>Bartonella</i> , <i>Mycoplasma pneumoniae</i> , and β -hemolytic streptococci); and immunizations (ie, hepatitis A/B/C, DTP, HiB, MMR, oral polio, and BCG)	Monomorphous pink to red papules and papulovesicles symmetrically on cheeks, extensor surfaces, and buttocks; trunk, palms, and soles often spared	Lichen planus, scabies, papular urticaria, lichenoid drug eruption, erythema multiforme, papular urticaria, and hand-foot-mouth disease	None
Hypersensitivity to mosquito bites	No	Asia (Japan, Taiwan, and Korea) and Central America (Mexico)	None	Erythema, bullae, necrosis, and ulceration at site of mosquito bites	None	Lymphoproliferative diseases: EBV-associated (NK/T cell leukemia/lymphoma) and non–EBV-associated (CLL and mantle cell lymphoma); CAEBV infection

Oral hairy leukoplakia	Yes	Immunosuppressed individuals (ie, HIV, solid organ transplant, etc)	None	Corrugated white to gray plaques on dorsolateral surface of the tongue; firmly adherent to mucosa	White sponge nevus, oral lichen planus, idiopathic leukoplakia, smoker's keratosis, and oral candidiasis	In HIV-positive individuals, predictive of progression to AIDS
Kikuchi–Fujimoto disease (histiocytic necrotizing lymphadenitis)	No	More common in Asia; women <40 years old	HHV-8, HIV, HTLV-1, dengue virus, <i>Yersinia enterocolitica</i> , <i>Bartonella</i> , <i>Brucella</i> , and <i>Toxoplasma</i>	Lymphadenopathy; nonspecific mucocutaneous findings (ie, ulcers and maculopapular eruption)	Kawasaki disease, infectious lymphadenitis, erythema multiforme, and SLE	Possible association with SLE
Hydroa vacciniforme	Yes	Worldwide (most cases reported in US, UK, Japan, and Europe); children	None	Recurrent vesiculopapules on sun-exposed areas; heal with pox-like scars; resolve in adolescence	Erythropoietic protoporphyrria, porphyria cutanea tarda, actinic prurigo, and polymorphous light eruption	None

BCG, Bacillus Calmette-Guérin; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; DTP, diphtheria, tetanus, and pertussis; HHV, human herpesvirus; Hib, *Haemophilus influenzae* type B; HSV, herpes simplex virus; HTLV-1, human T-lymphotrophic virus type 1; MMR, measles, mumps, and rubella; SLE, systemic lupus erythematosus.

azathioprine, thalidomide, cyclosporine, betacarotene, and fish oil supplementation have been used in HV with varying success.^{195–198} Patients with HV should be followed clinically for the development of atypical features, because lesions of typical HV have been reported to precede NK/T-cell lymphoma by up to 10 years.

Other manifestations

Additional rare cutaneous manifestations of EBV infection have been reported (Table III). The majority of these case reports describe cutaneous manifestations in patients with a clinical diagnosis of acute IM, but a pathogenic role of EBV in these conditions remains unclear.

The pathogenesis of drug eruption with eosinophils and systemic symptoms (DRESS) remains unclear, but appears to be multifactorial including ethnic predisposition, drug detoxification enzyme abnormalities, and viral reactivation.^{218,219} It has been proposed that drug-induced reactivation of EBV and other herpesviruses (ie, HHV-6, HHV-7, and CMV) within B-cell populations may lead to stimulation of virus-specific T-cell responses and exuberant cytokine production responsible for the clinical symptoms of DRESS.²¹³

Similar to HV-like lymphoma, patients with EBV-associated extranodal NK/T-cell lymphoma and lymphoproliferative disorder have presented with disseminated ulcerative papulonodular lesions mimicking pityriasis lichenoides et varioliformis acuta (PLEVA).²²⁰ In addition, cases of PLEVA have been reported without associated lymphoma in the setting of fulminant IM and reactivation of EBV infection.²⁰⁷ Recently, EBV has been shown to be present in a case of eosinophilic ulcer of the oral mucosa with CD30⁺ T lymphocytes expressing the EBV membrane protein.²²¹

CONCLUSION

EBV is a prototypic herpesvirus, resulting in lifelong infection by establishing latency in B lymphocytes. EBV infection is associated with a wide spectrum of clinical manifestations, ranging from self-limited mucocutaneous disease to aggressive malignancies (Table IV). It has been identified in a number of mucocutaneous diseases using PCR assays and EBER ISH, but a pathogenic role in many of these conditions remains uncertain. Although many patients with primary EBV infection initially present to pediatricians or primary care physicians, dermatologists should be able to recognize the mucocutaneous manifestations of infection, understand the relationship between virus

and host immune system, and be comfortable interpreting diagnostic tests for EBV.

REFERENCES

1. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis. *Proc Natl Acad Sci U S A*. 1968;59:94-101.
2. Williams H, Crawford DH. Epstein-Barr virus: the impact of scientific advances on clinical practice. *Blood*. 2006;107:862-869.
3. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet*. 1964;1:702-703.
4. Baer R, Bankier AT, Biggin MD, et al. DNA sequence and expression of the B95-8 Epstein-Barr virus genome. *Nature*. 1984;310:207-211.
5. Moghaddam A, Rosenzweig M, Lee-Parritz D, Annis B, Johnson RP, Wang F. An animal model for acute and persistent Epstein-Barr virus infection. *Science*. 1997;27:2030-2033.
6. Jenson HB. Epstein-Barr virus. *Pediatr Rev*. 2011;32:375-383.
7. Thorley-Lawson DA. Epstein-Barr virus: exploiting the immune system. *Nat Rev Immunol*. 2001;1:75-82.
8. Junker AK, Thomas EE, Radcliffe A, Forsyth RB, Davidson AG, Rymo L. Epstein-Barr virus shedding in breast milk. *Am J Med Sci*. 1991;302:220-223.
9. Israele V, Shirley P, Sixbey JW. Excretion of the Epstein-Barr virus from the genital tract of men. *J Infect Dis*. 1991;163:1341-1343.
10. Grose C. The many faces of infectious mononucleosis: the spectrum of Epstein-Barr virus infection in children. *Pediatr Rev*. 1985;7:35-44.
11. Luzuriaga K, Sullivan J. Infectious mononucleosis. *N Engl J Med*. 2010;362:1993-2000.
12. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6-19, 2003-2010. *PLoS One*. 2013;8:e64921.
13. Heath CW Jr, Brodsky AL, Potolsky AI. Infectious mononucleosis in a general population. *Am J Epidemiol*. 1972;95:46-52.
14. Sixbey JW, Shirley P. Epstein-Barr virus infection at mucosal surfaces: detection of genomic variants with altered pathogenic potential. *Springer Semin Immunopathol*. 1991;13:167-179.
15. Cheng CC, Chang LY, Shao PL, et al. Clinical manifestations and quantitative analysis of virus load in Taiwanese children with Epstein-Barr virus-associated infectious mononucleosis. *J Microbiol Immunol Infect*. 2007;40:216-221.
16. Frade R, Barel M, Ehlin-Henriksson B, Klein G. gp140, a C3b-binding membrane component of lymphocytes, is the B cell C3dg/C3d receptor (CR2) and is distinct from the neutrophil C3dg receptor (CR4). *Eur J Immunol*. 1985;15:1192-1197.
17. Fingeroth JD, Weis JJ, Tedder TF, Strominger JL, Biro PA, Fearon DT. Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. *Proc Natl Acad Sci U S A*. 1984;81:4510-4514.
18. Boman F, Gultekin H, Dickman PS. Latent Epstein-Barr virus infection in leiomyosarcomas. *Arch Path Lab Med*. 1997;121:834-838.
19. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. *Annu Rev Immunol*. 2007;25:587-617.
20. Levitsky V, Masucci MG. Manipulation of immune responses by Epstein-Barr virus. *Virus Res*. 2002;88:71-86.
21. Iwakiri D, Zhou L, Samantha M, et al. Epstein-Barr virus (EBV)-encoded small RNA is released from EBV-infected cells and activates signaling from Toll-like receptor 3. *J Exp Med*. 2009;206:2091-2099.
22. Gaudreault E, Fiola S, Olivier M, Gosselin J. Epstein-Barr virus induces MCP-1 secretion by human monocytes via TLR2. *J Virol*. 2007;81:8016-8024.
23. Fathallah P, Parroche H, Gruffat H, et al. EBV latent membrane protein 1 is a negative regulator of TLR9. *J Immunol*. 2010;185:6439-6447.
24. Rickinson AB, Moss DJ. Human cytotoxic T lymphocyte responses to Epstein-Barr virus infection. *Annu Rev Immunol*. 1997;15:405-431.
25. Hoshino Y, Morishima T, Kimura H, Nishikawa K, Tsurumi T, Kuzushima K. Antigen-driven expansion and contraction of CD8⁺-activated T cells in primary EBV infection. *J Immunol*. 1999;163:5735-5740.
26. Khyatti M, Patel PC, Stefanescu I, Menezes J. Epstein-Barr virus (EBV) glycoprotein gp350 expressed on transfected cells resistant to natural killer cell activity serves as a target antigen for EBV-specific antibody-dependent cellular cytotoxicity. *J Virol*. 1991;65:996-1001.
27. Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *N Engl J Med*. 2004;350:1328-1337.
28. Kieff E, Rickinson AB. Epstein-Barr Virus and its replication. In: Knipe DM, Howley PM, editors. *Fields virology*. 5th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2007.
29. Thorley-Lawson D. EBV persistence and latent infection in vivo. In: Robertson ES, editor. *Epstein-Barr virus*. 1st ed. Norfolk, UK: Caister Academic Press; 2005.
30. Niedobitek G, Agathangelou A, Herbst H, Whitehead L, Wright DH, Young LS. Epstein-Barr virus (EBV) infection in infectious mononucleosis: virus latency, replication and phenotype of EBV-infected cells. *J Pathol*. 1997;182:151-159.
31. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer*. 2004;4:757-768.
32. Saha A, Robertson ES. Epstein-Barr virus-associated B-cell lymphomas: pathogenesis and clinical outcomes. *Clin Cancer Res*. 2011;17:3056-3063.
33. Chen F, Zou JZ, Di Renzo L, et al. A subpopulation of normal B cells latently infected with Epstein-Barr virus resembles Burkitt lymphoma cells in expressing EBNA-1 but not EBNA-2 or LMP1. *J Virol*. 1995;69:3752-3758.
34. Yates JL, Warren N, Sugden B. Stable replication of plasmids derived from Epstein-Barr virus in various mammalian cells. *Nature*. 1985;313:812-815.
35. Saridakis V, Sheng Y, Sarkari F, et al. Structure of the p53 binding domain of HAUSP/USP7 bound to Epstein-Barr nuclear antigen 1 implications for EBV-mediated immortalization. *Mol Cell*. 2005;18:25-36.
36. Sivachandran N, Sarkari F, Frappier L. Epstein-Barr nuclear antigen 1 contributes to nasopharyngeal carcinoma through disruption of PML nuclear bodies. *PLoS Pathog*. 2008;4:e1000170.
37. Valentine R, Dawson CW, Hu C, et al. Epstein-Barr virus-encoded EBNA 1 inhibits the canonical NF-κB pathway in carcinoma cells by inhibiting IKK phosphorylation. *Mol Cancer*. 2010;9:1.
38. Wood VH, O'Neil JD, Wei W, Stewart SE, Dawson CW, Young LS. Epstein-Barr virus-encoded EBNA1 regulates cellular gene transcription and modulates the STAT1 and TGFβ signaling pathways. *Oncogene*. 2007;26:4135-4147.
39. Klein G. Viral latency and transformation: the strategy of Epstein-Barr virus. *Cell*. 1989;58:5-8.

40. Middeldorp JM, Brink AA, van den Brule AJ, Meijer CJ. Pathogenic roles for Epstein-Barr virus (EBV) gene products in EBV-associated proliferative disorders. *Crit Rev Oncol Hematol.* 2003;45:1-36.
41. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res.* 2004;10:803-821.
42. Rickinson AB. Chronic, symptomatic Epstein-Barr virus infection. *Immunol Today.* 1986;7:13-14.
43. Cohen JI, Jaffe ES, Dale JK, et al. Characterization and treatment of chronic active Epstein-Barr virus disease: a 28-year experience in the United States. *Blood.* 2011;117: 5835-5849.
44. Kimura H, Hoshino Y, Kanegae H, et al. Clinical and virologic characteristics of chronic active Epstein-Barr virus infection. *Blood.* 2001;98:280-286.
45. Boyd AS. Laboratory testing in patients with morbilliform viral eruptions. *Dermatol Clin.* 1994;12:69-82.
46. Felsenstein D, Carney WP, Iacoviello VR, Hirsh MS. Phenotypic properties of atypical lymphocytes in cytomegalovirus-induced mononucleosis. *J Infect Dis.* 1985; 152:198-203.
47. Win N, Davies SC. "Clover leaf" nuclei in atypical lymphocytes during acute *Toxoplasma gondii* infection. *Clin Lab Haematol.* 1990;12:111-112.
48. Hashimoto H, Maruyama H, Fujimoto K, Sakakura T, Seishu S, Okuda N. Hematologic findings associated with thrombocytopenia during the acute phase of exanthem subitum confirmed by primary human herpesvirus-6 infection. *J Pediatr Hematol Oncol.* 2002;24:211-214.
49. Paul JR, Bunnell WW. The presence of heterophile antibodies in infectious mononucleosis. *Am J Med Sci.* 1932; 183:90.
50. Basson V, Sharp AA. Monospot: a differential slide test for infectious mononucleosis. *J Clin Pathol.* 1969;22:324-325.
51. Evans AS. A prospective evaluation of heterophile and Epstein-Barr virus-specific IgM antibody tests in clinical and subclinical infectious mononucleosis: specificity and sensitivity of the tests and persistence of antibody. *J Infect Dis.* 1975;132:546-554.
52. Pitetti RD, Laus S, Wadowsky RM. Clinical evaluation of a quantitative real time polymerase chain reaction assay for diagnosis of primary Epstein-Barr virus infection in children. *Pediatr Infect Dis J.* 2003;22:736-739.
53. Cunha BA, Mickail N, Laguerre M. Babesiosis mimicking Epstein Barr virus (EBV) infectious mononucleosis: another cause of false positive monospot tests. *J Infect.* 2012;64: 531-532.
54. Vidrih JA, Walensky RP, Sax PE, Freedberg KA. Positive Epstein-Barr virus heterophile antibody tests in patients with primary human immunodeficiency virus infection. *Am J Med.* 2001;111:192-194.
55. Walensky RP, Rosenberg ES, Ferraro MJ, Losina E, Walker BD, Freedberg KA. Investigation of primary human immunodeficiency virus infection in patients who test positive for heterophile antibody. *Clin Infect Dis.* 2001;33:570-572.
56. Cohen JI. Clinical aspects of Epstein-Barr virus infection. In: Robertson ES, editor. *Epstein-Barr virus.* Norfolk, UK: Caister Academic Press; 2005. pp. 35-54.
57. Hess RD. Routine Epstein-Barr virus diagnostics from the laboratory perspective: still challenging after 35 years. *J Clin Microbiol.* 2004;42:3381-3387.
58. Henle G, Lennette ET, Alspaugh MA, Henle W. Rheumatoid factor as a cause of positive reactions in tests for Epstein-Barr virus specific IgM antibodies. *Clin Exp Immunol.* 1979;36: 415-422.
59. Dohno S, Maeda A, Ishiura Y, Sato T, Fujieda M, Wakiguchi H. Diagnosis of infectious mononucleosis caused by Epstein-Barr virus in infants. *Pediatr Int.* 2010;52:536-540.
60. Gartner BC, Kortmann K, Schäfer M, et al. No correlation in Epstein-Barr virus reactivation between serological parameters and viral load. *J Clin Microbiol.* 2000;38:2458.
61. Park JM, Shin JL, Lee JS, et al. False positive immunoglobulin M antibody to cytomegalovirus in child with infectious mononucleosis caused by Epstein-Barr virus infection. *Yonsei Med J.* 2009;50:713-716.
62. Miendje DY, Goubaud P, Bodeus M. False-positive IgM antibody tests for cytomegalovirus in patients with acute Epstein-Barr virus infection. *Eur J Clin Microbiol Infect Dis.* 2000;19:557-560.
63. Tranchand-Bunel D, Gras-Masse H, Bourez B, Dedecker L, Aurault C. Evaluation of an Epstein-Barr virus (EBV) immunoglobulin M enzyme-linked immunosorbent assay using a synthetic convergent peptide library, or mixotope, for diagnosis of primary EBV infection. *J Clin Microbiol.* 1999; 37:2366-2368.
64. Naveau S, Delfraissy JF, Poitrine A, Poynard T, Chaput JC. Simultaneous detection of IgM antibodies against the hepatitis A virus and the viral capsid antigen of Epstein-Barr virus in acute hepatitis. *Gastroenterol Clin Biol.* 1985;9:109-112.
65. Rhodes G, Smith RS, Rubin RE, Vaughan J, Horwitz CA. Identical IgM antibodies recognizing a glycine-alanine epitope are induced during acute infection with Epstein-Barr virus and cytomegalovirus. *J Clin Lab Anal.* 1990;4:456-464.
66. Fikar CR, McKee C. False positivity of IgM antibody to Epstein-Barr viral capsid antigen during acute hepatitis A infection. *Pediatr Infect Dis J.* 1994;13:413-414.
67. Aalto SM, Linnnavuori K, Peltola H, et al. Immunoreactivation of Epstein-Barr virus due to cytomegalovirus primary infection. *J Med Virol.* 1998;56:186-191.
68. van Essen GG, Lieverse AG, Sprenger HG, Schirm J, Weits J. False-positive Paul-Bunnell test in HIV seroconversion. *Lancet.* 1988;2:747-748.
69. Nystad TW, Myrmeal H. Prevalence of primary versus reactivated Epstein-Barr virus infection in patients with VCA IgG-, VCA IgM- and EBNA-1-antibodies and suspected infectious mononucleosis. *J Clin Virol.* 2007;38:292-297.
70. Jensen IP, Vestergaard BF. Assessment of the specificity of a commercial human parvovirus B19 IgM assay. *Clin Diagn Virol.* 1997;7:133-137.
71. Jenson HB. Virologic diagnosis, viral monitoring, and treatment of Epstein-Barr virus infectious mononucleosis. *Curr Infect Dis Rep.* 2004;6:200-207.
72. Holmes RD, Sokol RJ. Epstein-Barr virus and post-transplant lymphoproliferative disease. *Pediatr Transplant.* 2002;6:456-464.
73. Luderer R, Kok M, Niesters HG, Schuurman R, de Weerd O, Thijssen SF. Real-time Epstein-Barr virus PCR for the diagnosis of primary EBV infections and EBV reactivation. *Mol Diagn.* 2005;9:195-200.
74. Green M. Management of Epstein-Barr virus-induced post-transplant lymphoproliferative disease in recipients of solid organ transplantation. *Am J Transplant.* 2001;1:103-108.
75. Gulley ML. Molecular diagnosis of Epstein-Barr virus-related diseases. *J Mol Diagn.* 2001;3:1-10.
76. Ambinder RF, Mann RB. Detection and characterization of Epstein-Barr virus in clinical specimens. *Am J Pathol.* 1994; 145:239-252.
77. Brousset P, Meggetto F, Chittal S, et al. Assessment of the methods for the detection of Epstein-Barr virus nucleic acids

- and related gene products in Hodgkin's disease. *Lab Invest.* 1993;69:483-490.
78. Hamilton-Dutoit SJ, Pallesen G. Detection of Epstein-Barr virus small RNAs in routine paraffin sections using non-isotopic RNA/RNA in situ hybridization. *Histopathology.* 1994;25:101-111.
 79. Armstrong AA, Weiss LM, Gallagher A, et al. Criteria for the definition of Epstein-Barr virus association in Hodgkin's disease. *Leukemia.* 1992;6:869-874.
 80. Chadburn A, Ceserman E, Knowles DM. Molecular pathology of posttransplantation lymphoproliferative disorders. *Semin Diagn Pathol.* 1997;14:15-26.
 81. Niedobitek G, Herbst H. In situ detection of Epstein-Barr virus and phenotype determination of EBV-infected cells. *Methods Mol Biol.* 2006;326:115-137.
 82. Chen Y, Zheng X, Chen G, et al. Immunoassay for LMP1 in nasopharyngeal tissue based on surface-enhanced Raman scattering. *Int J Nanomedicine.* 2012;7:73-82.
 83. Li J, Zhang XS, Xie D, et al. Expression of immune-related molecules in primary EBV-positive Chinese nasopharyngeal carcinoma: associated with latent membrane protein 1 (LMP1) expression. *Cancer Biol Ther.* 2007;6:1997-2004.
 84. Hadinoto V, Shapiro M, Greenough TC, Sullivan JL, Luzuriaga K, Thorley-Lawson DA. On the dynamics of acute EBV infection and the pathogenesis of infectious mononucleosis. *Blood.* 2008;111:1420-1427.
 85. Farley DR, Zietlow SP, Bannon MP, Farnell MB. Spontaneous rupture of the spleen due to infectious mononucleosis. *Mayo Clin Proc.* 1992;67:846-853.
 86. Peter J, Ray CG. Infectious mononucleosis. *Pediatr Rev.* 1998; 19:276-279.
 87. McCarthy J, Hoagland RJ. Cutaneous manifestations of infectious mononucleosis. *JAMA.* 1964;187:193-194.
 88. Burger J, Thurau S, Haritoglou C. Bilateral lid swelling during infectious mononucleosis (Hoagland-sign). *Klin Monbl Augenheilkd.* 2005;222:1014-1016.
 89. Wu LY, Mesko JW, Petersen BH. Cold urticaria associated with infectious mononucleosis. *Ann Allergy.* 1983;50:271-274.
 90. Cseri-Gazdewich CM, Pendergrast JM, Reis M. Post-vaccination hyperhemolysis coinciding with remission of Epstein Barr virus (EBV)-associated immune thrombocytopenic purpura (ITP). *Am J Hematol.* 2009;84:612-613.
 91. Llorens-Terol J, Martinez-Roig A. Erythema nodosum associated with infectious mononucleosis. *Helv Paediatr Acta.* 1983;38:91-94.
 92. Sempau L, Valladares LM, Lomas-Garcia J, Alonso-Orcajo N. Garcia Ruiz de Morales JM, Rodriguez-Prieto MA. Pedunculated manifestation of infectious mononucleosis. *J Am Acad Dermatol.* 2012;67:e113-e114.
 93. Chovel-Sella A, Ben Tov A, Lahav E, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics.* 2013;131:e1424-e1427.
 94. Renn CN, Straff W, Dorfmuller A, Al-Masaoudi T, Merk HF, Sachs B. Amoxicillin- induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. *Br J Dermatol.* 2002;147:1166-1170.
 95. Jappe U. Amoxicillin-induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation. *Allergy.* 2007;62:1474-1475.
 96. Nazareth I, Mortimer P, McKendrick GD. Ampicillin sensitivity in infectious mononucleosis: temporary or permanent? *Scand J Infect Dis.* 1972;4:229-230.
 97. Wand JR, Perrotto JL, Isselbacher KJ. Circulating immune complexes and complement sequence activation in infectious mononucleosis. *Am J Med.* 1976;60:269-272.
 98. Bierman CW, Pierson WE, Zeitz SJ, Hoffman LS, VanArsdel PP Jr. Reactions associated with ampicillin therapy. *JAMA.* 1972; 220:1098-1100.
 99. Torre D, Tambini R. Acyclovir for treatment of infectious mononucleosis: a meta-analysis. *Scand J Infect Dis.* 1999;31: 543-547.
 100. Macsween KF, Higgins CD, McAulay KA, et al. Infectious mononucleosis in university students in the United Kingdom: evaluation of the clinical features and consequences of the disease. *Clin Infect Dis.* 2010;50:699-706.
 101. Rea TD, Russo JE, Katon W, Ashley RL, Buchwald DS. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract.* 2001;14:234-242.
 102. Halvorsen JA, Brevig T, Aas T, Skar AG, Slevolden EM, Moi H. Genital ulcers as initial manifestation of Epstein-Barr virus infection: two new cases and a review of the literature. *Acta Derm Venereol.* 2006;86:439-442.
 103. Rosman IS, Berk DR, Bayliss SJ, White AJ, Merritt DF. Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. *Pediatr Dermatol.* 2012;29: 147-153.
 104. Farhi D, Wendling J, Molinari E, et al. Non-sexually related acute genital ulcers in 13 pubertal girls: a clinical and microbiological study. *Arch Dermatol.* 2009;145: 38-45.
 105. Huppert JS, Gerber MA, Deitich HR, Mortensen JE, Staat MA, Adams Hillard PJ. Vulvar ulcers in young females: a manifestation of aphthosis. *J Pediatr Adolesc Gynecol.* 2006; 19:195-204.
 106. Martín JM, Godoy R, Caldúch L, Villalon G, Jordá E. Lipschütz acute vulval ulcers associated with primary cytomegalovirus infection. *Pediatr Dermatol.* 2008;25:113-115.
 107. Korting GW, Hinterberger G. Ulcus vulvae acutum with cold-agglutinin-positive, Mycoplasma-caused atypical pneumonia. *Hautarzt.* 1979;30:550-552.
 108. Chanal J, Carlotti A, Laude H, Wallet-Faber N, Avril MF, Dupin N. Lipschütz genital ulceration associated with mumps. *Dermatology.* 2010;221:292-295.
 109. Wetter DA, Bruce AJ, MacLaughlin KL, Rogers RS. Ulcus vulvae acutum in a 13-year-old girl after influenza A infection. *Skinmed.* 2008;7:95-98.
 110. Huppert JS. Lipschütz ulcers: evaluation and management of acute genital ulcers in women. *Dermatol Ther.* 2010;23: 533-540.
 111. Lehman JS, Bruce AJ, Wetter DA, Ferguson SB, Rogers RS. Reactive nonsexually related acute genital ulcers: review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol.* 2010;63: 44-51.
 112. Sárdy M, Wollenberg A, Niedermeier A, Flaig MJ. Genital ulcers associated with Epstein-Barr virus infection (ulcus vulvae acutum). *Acta Derm Venereol.* 2011;91:55-59.
 113. Barnes CJ, Alió AB, Cunningham BB, Friedlander SF. Epstein-Barr virus-associated genital ulcers: an under-recognized disorder. *Pediatr Dermatol.* 2007;24:130-134.
 114. Portnoy J, Ahronheim GA, Ghibu F, Clechner B, Joncas JH. Recovery of Epstein-Barr virus from genital ulcers. *N Engl J Med.* 1984;311:966-968.
 115. Brandt O, Abeck D, Gianotti R, Burgdorf W. Gianotti-Crosti syndrome. *J Am Acad Dermatol.* 2006;54:136-145.
 116. Gianotti F. L'acrodermatite papulosa infantile "malattia". *Gazz Sanit.* 1970;41:271-274.
 117. De Gaspari G, Bardare M, Constantino D. AU antigen in Crosti-Gianotti acrodermatitis. *Lancet.* 1970;1:1116-1117.

118. Hofmann B, Schuppe HC, Adams O, Lenard HG, Lehmann P, Ruzicka T. Gianotti-Crosti syndrome associated with Epstein-Barr virus infection. *Pediatr Dermatol.* 1997;14:273-277.
119. Schopf RE. Gianotti-Crosti syndrome in Epstein-Barr virus infection. *Hautarzt.* 1995;46:714-716.
120. Berger EM, Orlow SJ, Patel RR, Schaffer JV. Experience with molluscum contagiosum and associated inflammatory reactions in a pediatric dermatology practice: the bump that rashes. *Arch Dermatol.* 2012;148:1257-1264.
121. Magyarlaki M, Drobnitsch I, Schneider I. Papular acrodermatitis of childhood (Gianotti-Crosti disease). *Pediatr Dermatol.* 1991;8:224-227.
122. Smith KJ, Skelton H. Histopathologic features seen in Gianotti-Crosti syndrome secondary to Epstein-Barr virus. *J Am Acad Dermatol.* 2000;43:1076-1079.
123. Tokura Y, Tamura Y, Takigawa M, et al. Severe hypersensitivity to mosquito bites associated with natural killer cell lymphocytosis. *Arch Dermatol.* 1990;126:362-368.
124. Kawa K, Okamura T, Yagi K, Takeuchi M, Nakayama M, Inoue M. Mosquito allergy and Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disease. *Blood.* 2001;98:3173-3174.
125. Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol.* 2001;45:569-578.
126. Kunitomi A, Konaka Y, Yagita M. Hypersensitivity to mosquito bites as a potential sign of mantle cell lymphoma. *Intern Med.* 2005;44:1097-1099.
127. Asakura K, Kizaki M, Ikeda Y. Exaggerated cutaneous response to mosquito bites in a patient with chronic lymphocytic leukemia. *Int J Hematol.* 2004;80:59-61.
128. Park S, Bahng S, Kim EK, et al. Hodgkin's lymphoma arising in a patient with hypersensitivity to mosquito bites: a case report. *J Clin Oncol.* 2010;28:e148-e150.
129. Asada H. Hypersensitivity to mosquito bites: a unique pathogenic mechanism linking Epstein-Barr virus infection, allergy and oncogenesis. *J Dermatol Sci.* 2007;45:153-160.
130. Kanno H, Onodera H, Endo M, et al. Vascular lesion in a patient of chronic active Epstein-Barr virus infection with hypersensitivity to mosquito bites: vasculitis induced by mosquito bite with the infiltration of nonneoplastic Epstein-Barr virus-positive cells and subsequent development of natural killer/T-cell lymphoma with angiodesctruction. *Hum Pathol.* 2005;36:212-218.
131. Greenspan D, Greenspan JS, Conant M, Petersen V, Silverman S Jr, de Souza Y. Oral "hairy" leukoplakia in male homosexuals: evidence of association with both papillomavirus and a herpes-group virus. *Lancet.* 1984;2:831-834.
132. Bravo IM, Correnti M, Escalona L, et al. Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. *Med Oral Patol Oral Cir Bucal.* 2006;11:33-39.
133. Schmidt-Westhausen A, Gelderblom HR, Reichart PA. Oral hairy leukoplakia in an HIV-seronegative heart transplant patient. *J Oral Pathol Med.* 1990;19:192-194.
134. Schiødt M, Nørgaard T, Greenspan JS. Oral hairy leukoplakia in an HIV-negative woman with Behcet's syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1995;79:53-56.
135. Blomgren J, Bäck H. Oral hairy leukoplakia in a patient with multiple myeloma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1996;82:408-410.
136. Nicolatou O, Nikolatos G, Fisfis M, et al. Oral hairy leukoplakia in a patient with acute lymphocytic leukemia. *Oral Dis.* 1999;5:76-79.
137. Cho HH, Kim SH, Seo SH, et al. Oral hairy leukoplakia which occurred as a presenting sign of acute myeloid leukemia in a child. *Ann Dermatol.* 2010;22:73-76.
138. Duggal MS, Abudiak H, Dunn C, Tong HJ, Monyombwe T. Effect of CD4+ lymphocyte count, viral load, and duration of taking anti-retroviral treatment on presence of oral lesions in a sample of South African children with HIV+/AIDS. *Eur Arch Paediatr Dent.* 2010;11:242-246.
139. Greenspan D, Greenspan JS, Hearst NG, et al. Relation of oral hairy leukoplakia to infection with the human immunodeficiency virus and the risk of developing AIDS. *J Infect Dis.* 1987;155:475-481.
140. Schiødt M, Greenspan D, Daniels TE, Greenspan JS. Clinical and histologic spectrum of oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol.* 1987;64:716-720.
141. Sandvej K, Krenács L, Hamilton-Dutoit SJ, Rindum JL, Pindborg JJ, Pallesen G. Epstein-Barr virus latent and replicative gene expression in oral hairy leukoplakia. *Histopathology.* 1992;20:387-395.
142. Brandwein M, Nuovo G, Ramer M, Orlowski W, Miller L. Epstein-Barr virus reactivation in hairy leukoplakia. *Mod Pathol.* 1996;9:298-303.
143. Walling DM, Flaitz CM, Hosein FG, Montes-Walters M, Nichols CM. Effect of Epstein-Barr virus replication on Langerhans cells in pathogenesis of oral hairy leukoplakia. *J Infect Dis.* 2004;189:1656-1663.
144. D'Souza B, Rowe M, Walls D. The bfl-1 gene is transcriptionally upregulated by the Epstein-Barr virus LMP1, and its expression promotes the survival of a Burkitt's lymphoma cell line. *J Virol.* 2000;74:6652-6658.
145. Triantos D, Porter SR, Scully C, Teo CG. Oral hairy leukoplakia: clinicopathologic features, pathogenesis, diagnosis, and clinical significance. *Clin Infect Dis.* 1997;25:1392-1396.
146. Fernandez JF, Benito MA, Lizaldez EB, Montanes MA. Oral hairy leukoplakia: a histopathologic study of 32 cases. *Am J Dermatopathol.* 1990;12:571-578.
147. Greenspan JS, Greenspan D. Oral hairy leukoplakia: diagnosis and management. *Oral Surg Oral Med Oral Pathol.* 1989;67:396-403.
148. Herbst JS, Morgan J, Raab-Traub N, Resnick L. Comparison of the efficacy of surgery and acyclovir therapy in oral hairy leukoplakia. *J Am Acad Dermatol.* 1989;21:753-756.
149. Moura MD, Guimarães TR, Fonseca LM, de Almeida Pordeus I, Mesquita RA. A random clinical trial study to assess the efficiency of topical applications of podophyllin resin (25%) versus podophyllin resin (25%) together with acyclovir cream (5%) in the treatment of oral hairy leukoplakia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:64-71.
150. Schöfer H, Ochsendorf FR, Helm EB, Milbradt R. Treatment of oral 'hairy' leukoplakia in AIDS patients with vitamin A acid (topically) or acyclovir (systemically). *Dermatologica.* 1987;174:150-151.
151. Bhandarkar SS, Mackelfresh J, Fried L, Arbiser JL. Targeted therapy of oral hairy leukoplakia with gentian violet. *J Am Acad Dermatol.* 2008;58:711-712.
152. Goh BT, Lau RK. Treatment of AIDS-associated oral hairy leukoplakia with cryotherapy. *Int J STD AIDS.* 1994;5:60-62.
153. Kikuchi M. Lymphadenitis showing focal reticulum cervical hyperplasia with nuclear debris and phagocyte. *Acta Hematol Jpn.* 1972;35:379-380.
154. Fujimoto Y, Kojima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. *Naika.* 1972;30:920-927.

155. Bosch X, Guilabert A, Miquel R, Campo E. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. *Am J Clin Pathol.* 2004;122:141-152.
156. Yen A, Fearnleyhough P, Raimer SS, Hudnall SD. EBV-associated Kikuchi's histiocytic necrotizing lymphadenitis with cutaneous manifestations. *J Am Acad Dermatol.* 1997;36:342-346.
157. Atwater AR, Longley BJ, Aughenbaugh WD. Kikuchi's disease: case report and systematic review of cutaneous and histopathologic presentations. *J Am Acad Dermatol.* 2008;59:130-136.
158. Seong GM, Kim JH, Lim GC, Kim J. Clinicopathological review of immunohistochemically defined Kikuchi-Fujimoto disease—including some interesting cases. *Clin Rheumatol.* 2012;31:1463-1469.
159. Kim JH, Kim YB, In SI, Kim YC, Han JH. The cutaneous lesions of Kikuchi's disease: a comprehensive analysis of 16 cases based on the clinicopathologic, immunohistochemical, and immunofluorescence studies with an emphasis on the differential diagnosis. *Hum Pathol.* 2010;41:1245-1254.
160. Dorfman RF, Berry GJ. Kikuchi's histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol.* 1988;5:329-345.
161. Hollingsworth HC, Peiper SC, Weiss LM, Raffeld M, Jaffe ES. An investigation of the viral pathogenesis of Kikuchi-Fujimoto disease. Lack of evidence for Epstein-Barr virus or human herpesvirus type 6 as the causative agents. *Arch Pathol Lab Med.* 1994;118:134-140.
162. Ohshima K, Kikuchi M, Eguchi F, et al. Analysis of Epstein-Barr viral genomes in lymphoid malignancy using Southern blotting, polymerase chain reaction and in situ hybridization. *Virchows Arch B Cell Pathol.* 1990;59:383-390.
163. Anagnostopoulos I, Hummel M, Korbjahn P, Papadaki T, Anagnostou D, Stein H. Epstein-Barr virus in Kikuchi-Fujimoto disease. *Lancet.* 1993;341:893.
164. Rabado EM, Oliveira JF, da Cunha S, Corte-Real R, Melico-Silvestre AA. Kikuchi's disease associated with Epstein-Barr virus infection. *J Infect.* 1992;25:109-110.
165. Huh J, Chi HS, Kim SS, Gong G. A study of the viral etiology of histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease). *J Korean Med Sci.* 1998;13:27-30.
166. Takano Y, Saegusa M, Okudaira M. Pathologic analyses of non-overt necrotizing type Kikuchi and Fujimoto's disease. *Acta Pathol Jpn.* 1993;43:635-645.
167. Cho KJ, Lee SS, Khang SK. Histiocytic necrotizing lymphadenitis. A clinico-pathologic study of 45 cases with in situ hybridization for Epstein-Barr virus and hepatitis B virus. *J Korean Med Sci.* 1996;11:409-414.
168. George TI, Jones CD, Zehnder JL, Warnke RA, Dorfman RF. Lack of human herpesvirus 8 and Epstein-Barr virus in Kikuchi's histiocytic necrotizing lymphadenitis. *Hum Pathol.* 2003;34:130-135.
169. Huh J, Kang GH, Gong G, Kim SS, Ro JY, Kim CW. Kaposi's sarcoma-associated herpesvirus in Kikuchi's disease. *Hum Pathol.* 1998;29:1091-1096.
170. Vassallo J, Coelho Filho JC, Amaral VG. Histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis) in an HIV-positive patient. *Rev Inst Med Trop Sao Paulo.* 2002;44:265-268.
171. Bataille V, Harland CC, Behrens J, Cook MG, Holden CA. Kikuchi disease (histiocytic necrotizing lymphadenitis) in association with HTLV1. *Br J Dermatol.* 1997;136:610-612.
172. Harris VK, Danda D, Murali NS, et al. Unusual association of Kikuchi's disease and dengue virus infection evolving into systemic lupus erythematosus. *J Indian Med Assoc.* 2000;98:391-393.
173. Meyer O, Kahn MF, Grossin M, et al. Parvovirus B19 infection can induce histiocytic necrotizing lymphadenitis (Kikuchi's disease) associated with systemic lupus erythematosus. *Lupus.* 1991;1:37-41.
174. Feller AC, Lennert K, Stein H, Bruhn HD, Wuthe HH. Immunohistology and aetiology of histiocytic necrotizing lymphadenitis. Report of three instructive cases. *Histopathology.* 1983;7:825-839.
175. Chung JY, Kim SW, Han TH, Lim SJ. Detection of the *Bartonella henselae* gene sequence in lymph nodes of children with Kikuchi's disease. *Pediatrics.* 2005;115:1112.
176. Charalabopoulos K, Papalimneou V, Charalabopoulos A, Bai M, Agnantis N. *Brucella melitensis* infection stimulates an immune response leading to Kikuchi-Fujimoto disease. *In Vivo.* 2003;17:51-53.
177. Kikuchi M, Yoshizumi T, Nakamura H. Necrotizing lymphadenitis: possible acute toxoplasmic infection. *Virchows Arch A Pathol Anat Histol.* 1977;376:247-253.
178. Davies CW, Wathen CG. Kikuchi's disease and systemic lupus erythematosus. *Respir Med.* 1997;91:117-118.
179. Lopez C, Oliver M, Olavarria R, Sarabia MA, Chopite M. Kikuchi-Fujimoto necrotizing lymphadenitis associated with cutaneous lupus erythematosus: a case report. *Am J Dermatopathol.* 2000;22:328-333.
180. Iwatsuki K, Satoh M, Yamamoto T, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol.* 2006;142:587-595.
181. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood.* 2011;117:5019-5032.
182. Yesudian PD, Sharpe GR. Hydroa vacciniforme with oral mucosal involvement. *Pediatr Dermatol.* 2004;21:555-557.
183. Wierzbicka E, Malthieu F, Villers A, Guillet G. Oral involvement in hydroa vacciniforme. *Arch Dermatol.* 2006;142:651.
184. Jeng BH, Margolis TP, Chandra NS, McCalmont TH. Ocular findings as a presenting sign of hydroa vacciniforme. *Br J Ophthalmol.* 2004;88:1478-1479.
185. Sonnex TS, Hawk JL. Hydroa vacciniforme: a review of ten cases. *Br J Dermatol.* 1988;118:101-108.
186. Gu H, Chang B, Qian H, Li G. A clinical study on severe hydroa vacciniforme. *Chin Med J.* 1996;109:645-647.
187. Eramo LR, Garden JM, Esterly NB. Hydroa vacciniforme. Diagnosis by repetitive ultraviolet-A phototesting. *Arch Dermatol.* 1986;122:1310-1313.
188. Morizane S, Suzuki D, Tsuji K, Oono T, Iwatsuki K. The role of CD4 and CD8 cytotoxic T lymphocytes in the formation of viral vesicles. *Br J Dermatol.* 2005;153:981-986.
189. Iwatsuki K, Xu Z, Takata M, et al. The association of latent Epstein-Barr virus infection with hydroa vacciniforme. *Br J Dermatol.* 1999;140:715-721.
190. Iwatsuki K, Ohtsuka M, Akiba H, Kaneko F. Atypical hydroa vacciniforme in childhood: from a smoldering stage to Epstein-Barr virus-associated lymphoid malignancy. *J Am Acad Dermatol.* 1999;40:283-284.
191. Cho KH, Choi WW, Youn CS, Kim CW, Heo DS. Skin is the frequent site for involvement of peripheral T-cell and natural killer cell lymphomas in Korea. *J Dermatol.* 2000;27:500-507.
192. Cho KH, Kim CW, Heo DS, et al. Epstein-Barr virus-associated peripheral T-cell lymphoma in adults with hydroa vacciniforme-like lesions. *Clin Exp Dermatol.* 2001;26:242-247.
193. Hirai Y, Yamamoto T, Kimura H, et al. Hydroa vacciniforme is associated with increased numbers of Epstein-Barr virus-infected $\gamma\delta$ T cells. *J Invest Dermatol.* 2012;132:1401-1408.

194. Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. *Br J Dermatol.* 1995;132:956-963.
195. Rhodes LE, White SI. Dietary fish oil as a photoprotective agent in hydroa vacciniforme. *Br J Dermatol.* 1998;138:173-178.
196. Rhodes LE, Durham BH, Fraser WD, Friedmann PS. Dietary fish oil reduces basal and ultraviolet B-generated PGE2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol.* 1995;105:532-535.
197. Durbec F, Regulai Z, Leonard F, Pluot M, Bernard P. Efficacy of ω -3 polyunsaturated fatty acids for the treatment of refractory hydroa vacciniforme. *Pediatr Dermatol.* 2012;29:118-119.
198. Bruderer P, Shahabpour M, Christoffersen S, Andre J, Ledoux M. Hydroa vacciniforme treated by a combination of beta-carotene and canthaxanthin. *Dermatology.* 1995;190:343-345.
199. Drago F, Romagnoli M, Loi A, Rebora A. Epstein-Barr virus-related persistent erythema multiforme in chronic fatigue syndrome. *Arch Dermatol.* 1992;128:217-222.
200. Bodansky HJ. Erythema nodosum and infectious mononucleosis. *Br Med J.* 1979;2:1263.
201. Yokoyama S, Kasahara M, Fukuda A, Sato S, Koda F, Nakagawa A. Epstein-Barr virus-associated erythema nodosum after living-donor liver transplantation: a case report. *Liver Transpl.* 2009;15:446-448.
202. Hammar H. Erythema annulare centrifugum coincident with Epstein-Barr virus infection in an infant. *Acta Paediatr Scand.* 1974;63:788-792.
203. Ziemer M, Eisendle K, Zelger B. New concepts on erythema annulare centrifugum: a clinical reaction pattern that does not represent a specific clinicopathological entity. *Br J Dermatol.* 2009;160:119-126.
204. Park JY, Park JE, Kim YC. Generalized granuloma annulare possibly associated with acute Epstein-Barr virus infection. *Eur J Dermatol.* 2011;21:788-789.
205. Spencer SA, Fenske NA, Espinoza CG, Hamill JR, Cohen LE, Espinoza LR. Granuloma annulare-like eruption due to chronic Epstein-Barr virus infection. *Arch Dermatol.* 1988;124:250-255.
206. Song JE, Krunic AL. A rare variant of generalized granuloma annulare presenting with chronic Epstein-Barr virus infection: coincidence or association? *Acta Dermatovenerol Alp Panonica Adriat.* 2011;20:207-211.
207. Boss JM, Boxley JD, Summerly R, Sutton RN. The detection of Epstein-Barr virus antibody in 'exanthematic' dermatoses with special reference to pityriasis lichenoides. A preliminary survey. *Clin Exp Dermatol.* 1978;3:51-56.
208. Edwards BL, Bonagura VR, Valacer DJ, Ilowite NT. Mucha-Habermann's disease and arthritis: possible association with reactivated Epstein-Barr virus infection. *J Rheumatol.* 1989;16:387-389.
209. Klein PA, Jones EC, Nelson JL, Clark RA. Infectious causes of pityriasis lichenoides: a case of fulminant infectious mononucleosis. *J Am Acad Dermatol.* 2003;49(2 suppl case reports):S151-S153.
210. Marei A, Adler SP, Nigro G. Herpesvirus-associated acute urticaria: an age matched case-control study. *PLoS One.* 2013;8:e85378.
211. Arias-Santiago SA, Almazán-Fernández FM, Burkhardt-Pérez P, Naranjo-Sintes R. Cold urticaria associated with Epstein Barr virus mononucleosis. *Actas Dermosifiliogr.* 2009;100:435-436.
212. Baldari U, Raccagni AA, Celli B, Righini MG. Chronic bullous disease of childhood following Epstein-Barr virus seroconversion: a case report. *Clin Exp Dermatol.* 1996;21:123-126.
213. Camous X, Calbo S, Picard D, Musette P. Drug reaction with eosinophilia and systemic symptoms: an update on pathogenesis. *Curr Opin Immunol.* 2012;24:730-735.
214. Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol.* 2006;155:301-306.
215. Guissa VR, Aragão PA, Marques HH, Jacob CM, Silva CA. Chronic active Epstein-Barr virus infection mimicking Henoch-Schönlein purpura. *Acta Reumatol Port.* 2010;35:513-517.
216. Kanai K, Kuwabara S, Mori M, Arai K, Yamamoto T, Hattori T. Leukocytoclastic-vasculitic neuropathy associated with chronic Epstein-Barr virus infection. *Muscle Nerve.* 2003;27:113-116.
217. Nakagawa A, Ito M, Iwaki T, Yatabe Y, Asai J, Hayashi K. Chronic active Epstein-Barr virus infection with giant coronary aneurysms. *Am J Clin Pathol.* 1996;105:733-736.
218. Stander S, Metze D, Luger T, Schwarz T. Drug reaction with eosinophilia and systemic symptoms. *Hautarzt.* 2013;64:611-622.
219. Heymann WR. Addressing the role of human herpesviruses 6 and 7 in DRESS. *Skinmed.* 2014;12:100-101.
220. Hamada T, Nakamura S, Ko YH, et al. Epstein-Barr virus-associated T/natural killer-cell lymphomas in the elderly: the first consensus meeting in Kofu 2013. *J Dermatol.* 2014;41:40-42.
221. Abdel-Naser MB, Tsatsou F, Hippe S, et al. Oral eosinophilic ulcer, an Epstein-Barr virus-associated CD30+ lymphoproliferation? *Dermatology.* 2011;222:113-118.

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Epstein–Barr virus: Dermatologic associations and implications

Part II. Associated lymphoproliferative disorders and solid tumors

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Learning objectives

After completing this learning activity, participants should be able to identify lymphoproliferative disorders and malignant disorders associated with EBV, and describe the EBV-related diseases that occur in the immunocompromised host.

Disclosures

None declared.

Epstein–Barr virus (EBV) was the first human virus to be associated with oncogenesis. Over the past few decades, cumulative research has revealed that latent EBV infection may be implicated in the pathogenesis of a heterogeneous group of lymphoproliferative disorders and malignancies occurring in both immunocompetent and immunocompromised hosts. Many of these diseases have either primary or secondary cutaneous manifestations. Serologic studies and EBV-encoded RNA in situ hybridization stains have been used to show the association of EBV with disease; while these findings may imply a role, they do not equate with causation. In part II of this continuing medical education review, the salient features of EBV-associated lymphoproliferative disorders and solid tumors are detailed. (*J Am Acad Dermatol* 2015;72:21-34.)

Key words: angioimmunoblastic T-cell lymphoma; Burkitt lymphoma; diffuse large B-cell lymphoma; Epstein–Barr virus; gastric carcinoma; hemophagocytic syndrome; Hodgkin lymphoma; hydroa vacciniforme-like lymphoma; leiomyosarcoma; lymphomatoid granulomatosis; nasopharyngeal carcinoma; NK/T-cell lymphoma; posttransplant lymphoproliferative disorder.

INTRODUCTION

Epstein–Barr virus (EBV) has been associated with a range of lymphoproliferative disorders and solid tumors. It behoves both the dermatologist and dermatopathologist to understand these associations, because this knowledge may aid in the diagnosis, prognosis, and monitoring of disease. Serologic studies have been used to show an association with EBV, and for some diseases, titers may carry prognostic signif-

icance. EBV-encoded RNA (EBER) in situ hybridization (ISH) stains can be used to aid in the histologic diagnosis of EBV-associated malignancies. However, while these findings may imply a role and can aid in the diagnosis, they do not equate with causation. In part II of this continuing medical education article, the salient features of EBV-associated lymphoproliferative disorders and solid tumors are detailed (Table I).

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Abbreviations used:

AITL:	angioimmunoblastic T-cell lymphoma
BL:	Burkitt lymphoma
CAEBV:	chronic active Epstein–Barr virus
DLBCL:	diffuse large B-cell lymphoma
EBER:	Epstein–Barr virus–encoded RNA
EBNA:	Epstein–Barr virus nuclear antigen
EBV:	Epstein–Barr virus
ENK/T:	extranodal natural killer/T-cell lymphoma
HL:	Hodgkin lymphoma
HPS:	hemophagocytic syndrome
HRS:	Hodgkin and Reed–Sternberg-like
HV:	hydroa vacciniforme
HVLL:	hydroa vacciniforme–like lymphoma
ISH:	in situ hybridization
LMP1:	latent membrane protein-1
LYG:	lymphomatoid granulomatosis
MF:	mycosis fungoides
NHL:	non-Hodgkin lymphoma
PCR:	polymerase chain reaction
PTLD:	posttransplant lymphoproliferative disease
SPTCL:	subcutaneous panniculitis-like T-cell lymphoma
TIA-1:	T-cell intracellular antigen-1
VCA:	viral capsid antigen

MATURE B-CELL NEOPLASMS**Burkitt lymphoma****Key points**

- Burkitt lymphoma is an aggressive B-cell lymphoma that is subdivided into 3 categories: endemic, sporadic, and HIV-related
- Cutaneous involvement, presenting as erythematous nodules and plaques, is rare
- Endemic Burkitt lymphoma is the subtype that is most commonly associated with Epstein–Barr virus infection

Burkitt lymphoma (BL) is an aggressive, poorly differentiated B-cell lymphoma.^{1,2} It is the fastest growing tumor in humans, with an extremely short doubling time of 24 to 48 hours.³ BL is classified as a non-Hodgkin lymphoma and is further subdivided into 3 categories: endemic, sporadic, and HIV-related BL.^{3,4} Endemic BL most frequently arises in the head and neck, while sporadic BL usually presents with abdominal involvement, and HIV-related BL often affects the lymph nodes and bone marrow.⁴ Infrequently, cutaneous involvement occurs, presenting as well demarcated erythematous nodules and plaques.^{1,2} Skin disease results from both lymphatic and hematologic spread. Cutaneous lesions may also appear iatrogenically at sites of catheter insertion or previous surgical procedures.²

EBV was first discovered in cultured cell lines from endemic BL.^{3,5-7} However, the exact mechanisms linking EBV infection to lymphomagenesis are

not completely understood. EBV nuclear antigen 1 (EBNA1) is consistently expressed in endemic BL.³ Endemic BL is most closely associated with EBV infection; in areas where malaria is holoendemic (ie, Africa, Brazil, and Papua New Guinea), virtually all cases of endemic BL are associated with EBV infection.⁸ Coinfection with malaria increases the levels of circulating EBV, and children with antibodies against both EBV and *Plasmodium falciparum* have the highest risk of developing BL.^{3,9,10} While both EBV and *P falciparum* are acknowledged as cofactors in the development of endemic BL, the exact mechanisms are not entirely clear.¹¹ In contrast, EBV is present in only 30% of sporadic BL, and only 25% to 40% of tumors in patients with HIV-related BL.¹² In addition, BL contains translocations that activate the c-myc protooncogene, a key factor in the pathogenesis of BL.^{1,3,12}

Histologically, cutaneous BL is characterized by an atypical lymphocytic infiltrate in the dermis and subcutis composed of monomorphic, medium-sized, mitotically-active lymphocytes expressing CD20, CD79a, CD10, and BCL6.^{1,3,8,13} Tingible body macrophages containing apoptotic lymphocytes result in a “starry sky” appearance.³

BL follows an aggressive disease course but is potentially curable.¹² Chemotherapy is the mainstay of treatment, with an overall cure rate of approximately 90% in developed countries.³ Rituximab may be a useful adjunctive agent.³

Lymphomatoid granulomatosis**Key points**

- Lymphomatoid granulomatosis is an aggressive B-cell lymphoproliferative disorder that primarily affects the lungs
- Cutaneous findings include subcutaneous nodules, plaques, or ulcers, erythematous macular rashes, or erythroderma

Lymphomatoid granulomatosis (LYG) is a rare, aggressive, angioinvasive lymphoproliferative disorder of EBV⁺ B cells associated with a large population of reactive, infiltrating T cells.^{14,15} Lung involvement is present in nearly all patients, but other organs may also be affected, including the kidneys, liver, central nervous system, or skin.^{16,17} Cutaneous lesions occur in >40% of patients and include subcutaneous nodules, plaques, or ulcers, erythematous macular rashes, or erythroderma.¹⁸⁻²³ Not uncommonly, these cutaneous findings may represent the first sign of disease.²⁰⁻²² Middle-aged adults are most commonly affected.²⁴

Table I. Lymphoproliferative disorders commonly associated with Epstein–Barr virus

Disease	Demonstration of EBV in tissue	Epidemiology	Other possible etiologies	Cutaneous findings	Latency
Burkitt lymphoma	Yes	Found worldwide; endemic Burkitt lymphoma in Africa, Brazil, and Papua New Guinea; affects children, the immunosuppressed, and patients with HIV	c-myc translocation	Erythematous nodules and plaques	I
Lymphomatoid granulomatosis	Yes	Found in Western countries; affects adults	Immunodeficiency disorders	Subcutaneous nodules, plaques, or ulcers, erythematous macular rashes, or erythroderma	II
EBV ⁺ diffuse large B-cell lymphoma of the elderly	Yes	Found in Asia more than in Western countries; affects elderly adults	Immunosenescence	Erythematous papules or subcutaneous nodules	II, III
Extranodal natural killer/T-cell lymphoma	Yes	Found in Asia and Central and South America, uncommon in Europe and North America; affects adults	—	Erythematous patches, papules, nodules, tumors, ulcerations, and cellulitis	II
Hydroa vacciniforme-like lymphoma	Yes	Found in Asia and Central and South America; affects children	—	Vesicopapules, facial edema, large ulcers, severe scarring, and disfigurement	—
Angioimmunoblastic lymphoma	Yes	Found worldwide; affects middle-aged adults and the elderly	Human herpesvirus-6	Macular and papular eruptions, nodules, plaques, ulcerations, petechiae, or urticaria	II
Hodgkin lymphoma	Yes	Found worldwide; has a bimodal age distribution	—	Papules, nodules, asteatosis, and eczema	II
Posttransplant lymphoproliferative disorder	Yes	Found worldwide; affects transplant recipients and whites more than African Americans	—	Erythematous plaques, nodules, or tumors on the face, trunk, and extremities, and erythroderma	III
Hemophagocytic syndrome	Yes	Found in Asia; more common in children	Variety of viruses, bacteria, mycobacteria, fungi, or parasites	Nonspecific transient generalized macular eruption, erythroderma, and purpuric macules or papules	—

EBV, Epstein–Barr virus.

The majority of patients with LYG do not have an obvious preexisting immunodeficiency; however, immune surveillance is often defective as evidenced by below normal numbers of CD4 and CD8 T cells in many patients at the time of diagnosis.^{17,20} LYG has also been reported in patients with autoimmune disease and congenital immunodeficiencies.²⁰ Yazdi

et al¹⁸ reported a case of LYG that occurred after treatment with imatinib.

Microscopic evaluation of biopsy specimens obtained from both the skin and lungs reveal a mononuclear infiltrate of small and large lymphocytes demonstrating angioinvasion and angiodesctruction.^{14,18} Infarct-like tissue necrosis and fibrinoid

necrosis may be present.¹⁶ Small T cells and histiocytes predominate, but well-formed granulomas are usually absent, despite the entity's name. The majority of cases also display a smaller population of large, CD20⁺ atypical B cells that exhibit positivity for EBV.^{14,19} Latent membrane protein-1 (LMP1) may be positive in this population of atypical cells; however, skin biopsy specimens may lack atypical lymphoid cells.^{20,25}

The clinical behavior of LYG varies from an indolent process to an aggressive lymphoma, with outcomes ranging from spontaneous regression to death, which most often results from progressive pulmonary involvement.²⁵ For patients who have constitutional symptoms or multiorgan involvement, the prognosis is usually poor.²⁵ Treatment is guided by the patient's grade of disease, ranging from systemic corticosteroids and interferon-alfa-2b to rituximab, and multiagent chemotherapy in the most aggressive cases.^{20,24}

Age-related Epstein–Barr virus–associated B-cell lymphoproliferative disorders

Key points

- **EBV⁺ diffuse large B-cell lymphoma of the elderly is an aggressive EBV⁺ monoclonal B-cell lymphoproliferative disorder arising in elderly immunocompetent individuals**
- **EBV⁺ mucocutaneous ulcers occur in the oropharyngeal mucosa, skin, and gastrointestinal tract and are associated with immunosuppressive medications or age-related immunosenescence**

EBV⁺ diffuse large B-cell lymphoma of the elderly. EBV⁺ diffuse large B-cell lymphoma (DLBCL) of the elderly is an age-related EBV⁺ monoclonal B-cell lymphoproliferative disorder arising in adults >50 years of age (with a median age of 71 years) without any known immunodeficiency or previous lymphoma.^{26–28} It was initially described by Oyama et al²⁹ in 2003, who evaluated the clinical and histologic characteristics of EBV-associated B-cell lymphoproliferative disorders in 22 patients without predisposing immunodeficiencies.²⁹ Subsequently, EBV-positive DLBCL of the elderly was recognized as a provisional entity in the 2008 World Health Organization classification system.²⁸ The majority of patients present with extranodal disease; sites of involvement include the skin and soft tissue, bone/bone marrow, nasal and oropharyngeal cavities, lung, tonsils, and gastrointestinal system.³⁰ Cases of primary cutaneous involvement have been reported,

presenting as erythematous papules or subcutaneous nodules.^{31,32}

Polymorphic and monomorphic/large-cell subtypes have been described, although both histologic patterns may be present in the same specimen. The polymorphous subtype displays a broad range of B-cell maturation and contains reactive cells (ie, lymphocytes, plasma cells, and histiocytes), while the monomorphic/large-cell variant contains a uniform population of large cells.³³ Varying numbers of centroblasts, immunoblasts, and Hodgkin and Reed–Sternberg (HRS)–like cells are present.³⁴ The neoplastic cells express B-cell antigens (ie, CD19, CD20, CD79a, and PAX5) as well as MUM1/IRF4, BCL2, CD20 and EBER ISH, while they are negative for BCL6 and CD10. EBV positivity has also been noted in cutaneous infiltrates.³² Large areas of tissue necrosis may be present.^{28,29,34}

LMP1 expression is present in >90% of cases, while EBNA2 is present in <33% of cases.^{30,33} Immunosenescence may also play a role in pathogenesis, because B cell diversity and the absolute number of T lymphocytes decrease with age.^{27,30}

EBV⁺ DLBCL follows a rapidly deteriorating clinical course, with a median survival of 2 years.^{26,30} Histologic identification of EBV by immunohistochemistry aids in the diagnosis of DLBCL of the elderly, and also has prognostic significance. Patients with EBV⁺ DLBCL have a poorer overall survival, treatment response, and progression-free survival when compared to patients with EBV[−]DLBCL.^{26,35}

Rituximab and combination chemotherapy, the current standard therapy for DLBCL, has also been used for EBV⁺ DLBCL of the elderly.^{26,33} Unfortunately, outcome data for this regimen are limited, and novel therapies may be required to treat this aggressive disease.

EBV⁺ “mucocutaneous ulcer”. In, 2010 Dojcinov et al³⁶ described a series of 26 patients with EBV⁺ circumscribed mucocutaneous ulcerations involving the oropharyngeal mucosa, skin, and gastrointestinal tract that were associated with either immunosuppressive medications or age-related immunosenescence. Biopsy specimens of these ulcerations are characterized by a polymorphous infiltrate with atypical immunoblasts, which often displayed an HRS-like cell morphology. Monoclonal T cell gene rearrangement is present in nearly 40% of cases. These lesions follow an indolent disease course, often with spontaneous regression. Treatment has also included chemotherapy and radiation.³⁶ At this time, no disease-associated deaths have been reported.³⁶

Age-related EBV-associated B-cell lymphoproliferative disorders: A spectrum of disease? More recently, Dojcinov et al³⁷ further explored age-related EBV-associated B-cell lymphoproliferative disorders and categorized them into 4 groups: (1) reactive lymphoid hyperplasia; (2) polymorphic extranodal or (3) polymorphic nodal lymphoproliferative disease; and (4) diffuse large B-cell lymphoma. Disease-specific 5-year survival rates were 100%, 93%, 57%, and 25%, respectively. These results support the hypothesis that a spectrum of disease age-related EBV-associated B-cell lymphoproliferative disorders exist. Ultimately, it may be prudent to work collaboratively with oncologists to assess for systemic involvement and formulate a therapeutic plan.

MATURE T CELL AND NATURAL KILLER CELL NEOPLASMS

Extranodal natural killer/T-cell lymphoma, nasal type

Key points

- **Extranodal natural killer/T-cell lymphoma is an aggressive hematologic disorder that is subcategorized into nasal or extranasal according to the anatomic site of primary disease involvement**
- **Cutaneous lesions include erythematous patches, papules, nodules, tumors, ulcers, and cellulitis**

Extranodal NK/T-cell lymphoma (ENK/T) is an aggressive hematologic malignancy that is endemic in Asia and parts of Central and South America. It rarely occurs in Europe and North America.³⁸⁻⁴¹ Middle-aged adults are most commonly affected.^{42,43} ENK/T is subcategorized into nasal and extranasal ENK/T according to the anatomic site of primary disease involvement.⁴² Nasal ENK/T most commonly arises in the upper aerodigestive tract and presents with upper respiratory tract symptoms, including nasal obstruction, sinusitis, epistaxis, facial swelling, and destructive midfacial lesions ("lethal midline granuloma").³⁸ Extranasal ENK/T can occur in a number of sites, preferentially involving the skin, soft tissue, gastrointestinal tract, and testes.^{38,39,44-46} Cutaneous lesions frequently occur and consist of erythematous patches, papules, nodules, tumors, ulcerations, and cellulitis (Fig 1, A).^{41,42,47-50} Lymph node and bone marrow involvement are uncommon.^{40,46}

Regardless of the patient's ethnicity, NK/T-cell lymphoma is strongly associated with EBV.⁴⁶ This association was first described by Harabuchi et al⁵¹ in 1990, who found EBV positivity in tumor cells and

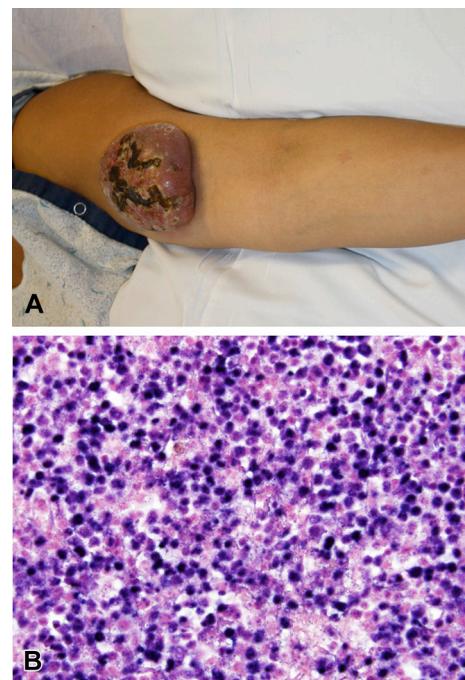


Fig 1. **A**, Erythematous exophytic tumor with central ulceration, necrosis, and serous crust on the upper arm of a patient with extranasal, extranodal natural killer/T-cell lymphoma. **B**, Positive Epstein–Barr virus–encoded RNA in situ hybridization. (**A**, Photograph courtesy of Justin Green, MD; **B**, photograph courtesy of Jeanette Camacho, MD.)

noted elevated antibody titers to EBV in affected patients.⁵¹ In addition, plasma EBV DNA can be used to monitor disease activity; a higher titer is associated with decreased disease-free survival.⁵²

The histopathologic examination reveals a proliferation of atypical lymphocytes with an angiocentric and angioinvasive growth pattern.^{38,41,43} Cytologically, the tumor cells may be small, medium, large, or anaplastic.^{40,46} Zonal necrosis may be prominent.^{38,40} Neoplastic cells express cytotoxic granule proteins, including T-cell intracellular antigen-1 (TIA-1), granzyme B, and perforin. In addition, the cells are CD2⁺, cytoplasmic CD3⁺, CD56⁺, and EBER ISH⁺ (Fig 1, B).³⁸ MIB1 (Ki-67) reveals a high proliferative index.

Overall, the prognosis of ENK/T is variable. While patients in the early stages of the disease tend to respond well to therapy, patients with late-stage disease often have a dismal prognosis.⁴⁶ When compared to nasal ENK/Ts, extranasal ENK/Ts have more aggressive clinical features, a poor response to therapy, and poorer overall survival.⁵³ Better survival outcomes are seen in patients with localized cutaneous disease.^{42,45,54,55} Chemotherapy and radiation are the mainstays of treatment.

Hydroa vacciniforme–like lymphoma**Key points**

- **Hydroa vacciniforme–like lymphoma is a cutaneous T-cell lymphoma that occurs predominantly in children and adolescents from Asia, Central America, South America, and Mexico**
- **Patients with hydroa vacciniforme–like lymphoma present with vesiculopapules, marked facial edema, large ulcerative cutaneous lesions, hemorrhagic bullae, atrophic scars, and severe disfigurement in both sun-exposed and photoprotected areas**
- **Lesions contain monoclonal T-cell receptor gene rearrangements**

Hydroa vacciniforme-like lymphoma (HVLL) is a rare EBV⁺ cutaneous T-cell lymphoma occurring predominantly in children and adolescents from Asia, Central America, South America and Mexico.^{56,57} In addition to the characteristic vesiculopapules of classical hydroa vacciniforme (HV), HVLL presents with marked facial edema, large ulcerative cutaneous lesions, hemorrhagic bullae, atrophic scars, and severe disfigurement in both sun-exposed and photoprotected areas.^{56,58-60} Unlike HV, lesions are not induced by sun exposure and typically do not resolve spontaneously with age.⁶¹ In some cases, patients have systemic complications and laboratory abnormalities, including intermittent fever, hepatosplenomegaly, and lymphadenopathy.⁵⁶⁻⁵⁸ HVLL was initially considered to be a severe, atypical variant of HV, but subsequent research revealed that the majority of lesions contain monoclonal T-cell receptor gene rearrangements.^{56,57,59} HVLL was first recognized in the 2008 World Health Organization classification system as one of the EBV⁺ lymphoproliferative diseases of childhood.⁵⁷

EBV-viral capsid antigen (VCA) antibodies have been reported, suggesting a close pathogenic relationship with chronic active EBV infection.^{58,62,63} Hypersensitivity to mosquito bites has a similar geographic distribution, and has been reported in patients with severe HV-like eruptions, leading some to suggest a shared pathogenesis.⁶⁴

The microscopic evaluation of cutaneous lesions reveals a perivascular and periadnexal lymphocytic infiltrate of atypical small to medium cells in the papillary and reticular dermis, occasionally extending into the subcutis.^{58,60} Vasculitis, angiodestruction, and necrosis may also be present.^{57,65} Neoplastic cells often have a CD8⁺ cytotoxic T-cell phenotype, expressing TIA-1, granzyme B, or perforin.^{56,62} Less commonly, cells are CD56⁺,

indicating an NK/T-cell phenotype.^{57,58,62} In cases with an NK/T-cell phenotype, the lymphocytic infiltrate often involves the subcutis, mimicking subcutaneous panniculitis-like T-cell lymphoma (SPTCL).⁵⁶ Rare cases of CD4⁺ cytotoxic T-cell phenotype have been reported.⁵⁹ EBER ISH is consistently positive, while LMP1 is only expressed occasionally.^{56,58,61}

HVLL follows a variable disease course; recurrent skin lesions, intermittent fever, and hepatosplenomegaly may persist.^{62,65} A more aggressive clinical course is associated with progression to the hemophagocytic syndrome and NK/T-cell lymphoma.^{56,57,63} High titers of antibodies to EBV are predictive of progressive disease and a poor prognosis.⁶² This entity is relatively rare, and standardized treatment protocols have not been developed. Therapies that have been used previously in the treatment of HVLL include interferon-alfa, systemic steroids, cyclosporine, intravenous immunoglobulin, combination chemotherapy, and radiation.^{58,61,66}

Angioimmunoblastic T-cell lymphoma**Key point**

- **Up to 50% of patients withAITL develop nonspecific cutaneous findings, including macular and papular eruptions, nodules, plaques, ulcerations, petechiae, or urticaria**

Angioimmunoblastic T-cell lymphoma (AITL) is one of the most common subtypes of peripheral T-cell lymphoma, predominantly occurring in middle-aged adults and the elderly.⁶⁷⁻⁶⁹ Clinically, the majority of patients present with symptoms of both nodal and extranodal disease, characterized by lymphadenopathy, hepatosplenomegaly, and constitutional symptoms (ie, fever, chills, and night sweats).⁶⁷ Up to 50% of patients with AITL develop nonspecific cutaneous findings, including macular and papular eruptions, nodules, plaques, ulcerations, petechiae, or urticaria.^{68,70} Martin et al⁷¹ reported a case of systemic AITL presenting with granuloma annulare-like lesions. Laboratory abnormalities may include polyclonal hypergammaglobulinemia, an elevated lactate dehydrogenase level, cold agglutinins with hemolytic anemia, a positive rheumatoid factor, and anti-smooth muscle antibodies.⁶⁸⁻⁷⁰

EBV is frequently detected in biopsy specimens that have been obtained from lymph nodes; evidence of EBV by ISH or polymerase chain reaction (PCR) studies may be seen in up to 96% of cases.⁷² However, EBER ISH has revealed that the EBV⁺ cells are CD79a⁺ B cells, distinct from the



Fig 2. Hyperpigmented erythematous plaque in a patient with subcutaneous panniculitis-like T-cell lymphoma. (Photograph courtesy of Dirk Elston, MD.)

neoplastic T cell population.^{69,73} This finding raises the possibility that EBV may be reactivated in the presence of immunodeficiency as a consequence of AITL, rather than contributing to the pathogenesis of the disease itself.⁷³ Human herpesvirus-6 (HHV-6) has also been implicated as an etiologic agent in the development in AITL; Zhou et al⁷³ performed PCR on archived tissue specimens of AITL and found evidence of EBV and HHV-6 in 86% and 45% of cases, respectively.⁷³

Histopathologic examination reveals partial or complete effacement of the lymph node architecture by a mixed cellular infiltrate.⁷⁴ The vast majority of cases consist of small to medium-sized CD4⁺ T cells with monoclonal T-cell receptor gene rearrangements.^{74,75} Ponciano et al⁷⁶ reported a case of relapsed AITL presenting as erythematous plaques that mimicked mycosis fungoides histologically with a CD4⁺ T-cell epidermotropic infiltrate.

AITL has a poor prognosis, with a median survival of <3 years.^{67,77} Patients are at an increased risk for opportunistic infections.^{67,69} In 1 case report, serum EBV load was reported to correlate with disease burden and treatment response.⁷⁸ However, subsequent studies of patients with AITL have found no correlation between EBV positivity and prognosis.^{74,77} Treatment involves combination chemotherapy, radiation, or autologous stem cell transplantation.⁷⁹

Subcutaneous panniculitis-like T-cell lymphoma

Key point

- While the majority of sporadic subcutaneous panniculitis-like T-cell lymphomas are not associated with Epstein–Barr virus, cases of Epstein–Barr virus positivity have been rarely reported, particularly in Asian patients

SPTCL is a rare, cutaneous, cytotoxic alpha/beta T-cell lymphoma.⁸⁰ Clinically, it presents as violaceous subcutaneous nodules and infiltrated

plaques that involve the trunk and extremities, occasionally with secondary ulceration or associated pruritus (Fig 2).^{80–82}

While the majority of sporadic SPTCLs are not associated with EBV, cases of EBV positivity have been rarely reported, particularly in Asian patients.⁸¹ Nemoto et al⁸³ reported a case of SPTCL occurring in a patient with rheumatoid arthritis treated with methotrexate that was positive for LMP1 ISH.⁸³ Whether EBV actually plays a role in the etiology of SPTCL or represents a coincidental finding remains uncertain.⁸²

The histopathology of SPTCL specimens reveals infiltration of the subcutis by small to medium-sized atypical lymphocytes that rim adipocytes in a wreath-like manner.⁸¹ According the World Health Organization classification, SPTCL has a CD3⁺/CD4⁻/CD8⁺ phenotype, often expressing cytotoxic proteins (ie, TIA-1, granzyme, or perforin).^{81,84} Tumor cells are positive for T-cell receptor beta F1 and CD56⁻, helping to differentiate SPTCL from primary cutaneous gamma/delta T-cell lymphoma.⁸⁵

Patients with SPTCL have a protracted clinical course with a favorable prognosis, occasionally with spontaneous regression.^{82,84} A small percentage of cases may consequently develop hemophagocytic syndrome, resulting in a more aggressive course and poorer prognosis.^{80,84} Treatments include immunosuppressive therapy (ie, prednisone or cyclosporine), radiotherapy, or combination chemotherapy.⁸²

Mycosis fungoides

Key point

- The association of Epstein–Barr virus with mycosis fungoides is controversial because the data are conflicting

In patients with mycosis fungoides (MF) and Sézary syndrome, antibodies against EBV antigens are more frequent, and higher titers are present when compared to control populations.^{86,87} In addition, EBV positivity has been shown in tumoral lymphocytes of MF lesions via ISH and PCR.⁸⁸ However, conflicting evidence exists; other studies have failed to identify EBV in lesions of MF.^{89–91} It therefore remains controversial as to whether or not EBV is indeed an etiologic agent in the development of MF.

HODGKIN LYMPHOMA

Key points

- Hodgkin lymphoma is a malignant B-cell lymphoma that usually presents with painless lymphadenopathy
- Epstein–Barr virus is most commonly associated with the mixed cellular subtype of classic Hodgkin lymphoma

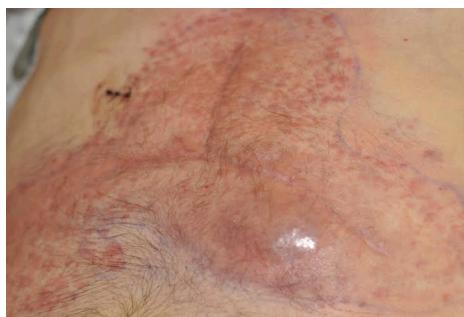


Fig 3. Coalescing erythematous papules and nodules on the abdomen of a patient with posttransplant lymphoproliferative disorder. (Photograph courtesy of Misha Rosenbach, MD.)

- **Cutaneous findings of Hodgkin lymphoma include papules, nodules, asteatosis, and eczema**

Hodgkin lymphoma (HL), previously known as Hodgkin disease, is a malignant B-cell lymphoma characterized by the presence of Hodgkin and Reed–Sternberg (HRS) cells.⁹² HL usually presents with painless lymphadenopathy above the diaphragm, and possibly “B-symptoms,” including cyclic fevers, night sweats, weight loss, and fatigue. Skin involvement is uncommon and usually occurs in the late stages of disease.⁹³ Cutaneous findings include papules, nodules, asteatosis, and eczema.^{93,94} Primary cutaneous HL is extremely rare, but has been reported.^{93,94}

The incidence of HL follows a bimodal age curve, with a peak in young adults, particularly males.⁹⁵ HL is found worldwide, but it is more common in developed countries.⁹⁵ EBV-associated HL, in particular, is more common in children and older adults.⁹⁶

Classic HL, which accounts for 95% of cases of HL, is subdivided into 4 histologic subtypes: (1) nodular sclerosis; (2) mixed cellularity; (3) lymphocyte-rich; and (4) lymphocyte-depleted.^{92,95} Biopsy specimens reveal effacement of lymph node architecture by a small number of HRS cells amidst a background of reactive nonneoplastic inflammatory cells.⁹⁵ In patients with classic HL, HRS cells express CD15 and CD30, rarely express B-cell markers, and are CD45⁻.⁹² Cases of HL containing EBV are most commonly the mixed cellular subtype, followed by the nodular sclerosing subtype.^{95,97–99}

EBV has long been suspected to be an etiologic agent in the development of HL, and considerable evidence has substantiated this hypothesis. Initially, numerous studies revealed that patients with HL have higher antibody titers specific for EBV antigens than control subjects.^{97,100,101} Weiss et al¹⁰⁰ first detected EBV DNA by Southern blot

DNA hybridization in tissues from patients with HL. Subsequently, ISH and immunohistochemical studies localized EBV to the malignant HRS cells.^{97,100} In developed countries, up to 40% to 50% of cases of HL are associated with EBV.^{96,99}

The prognosis of HL is variable, and advances in therapy over the last several decades have led to increased survival rates. Current treatment regimens for HL may include combination chemotherapy and radiation. The 5-year survival rate for patients who are ≥ 65 years of age is 52%, compared to 97% in patients ≤ 19 years of age and 89% in patients between 20 and 64 years of age.¹⁰²

IMMUNODEFICIENCY-RELATED LYMPHOPROLIFERATIVE DISORDERS

Posttransplant lymphoproliferative disorder

Key point

- **Posttransplant lymphoproliferative disorder encompasses a heterogeneous group of lymphoid proliferations ranging from polyclonal plasmacytic hyperplasia to non-Hodgkin lymphoma**

Posttransplant lymphoproliferative disorder (PTLD) encompasses a heterogeneous group of lymphoid neoplasms occurring in the posttransplant setting, ranging from polyclonal plasmacytic hyperplasia (infectious mononucleosis-like PTLD) to monoclonal lymphoproliferative disorders (often non-Hodgkin lymphoma).^{13,103–106} Patients with both solid organ and bone marrow transplants may be affected, and the incidence varies with organ type and severity of immunosuppression.^{4,107} The highest risk for developing PTLD includes patients with heart, lung, intestinal, and multiorgan transplants.¹⁰⁸ Most PTLDs occur within the first year posttransplantation.^{8,109,110}

PTLD often occurs in extranodal sites, most commonly affecting the anatomic region of the transplanted organ or the organ itself.^{105,111,112} The clinical features are nonspecific, and lymphadenopathy may be absent. Cutaneous involvement is considerably rare, presenting as erythematous plaques, nodules, or tumors on the face, trunk, and extremities (Fig 3).^{105,106,112} Erythroderma has also been reported.¹⁰⁶

The majority of PTLDs are of B-cell origin, and >90% of B-cell PTLDs are associated with EBV infection.^{4,103,104,107} Histopathology reveals a dense proliferation of atypical lymphocytes with large nuclei and prominent mitotic figures.^{105,106}

The outcome of PTLD is poor; the 1-year mortality in renal transplants was 40% and in heart transplant recipients was 50%.¹¹¹ Treatment options for PTLD include reducing immunosuppressive therapy,

acyclovir, immunoglobulin, systemic steroids, rituximab, interferon-alfa 2b, and chemotherapy.^{105,106}

Methotrexate-associated lymphoproliferative disease

Key point

- **Methotrexate is associated with a heterogeneous group of Epstein–Barr virus–positive lymphoproliferative disorders**

Treatment with methotrexate is associated with EBV⁺ lymphoma more frequently than alternative immunosuppressive agents.¹⁵ Cases of primary cutaneous methotrexate-associated lymphoproliferative disease have included DLBCL, SPTCL, and intraoral ulcerations histologically resembling Hodgkin lymphoma.^{15,83,113} Lesions may spontaneously regress after the discontinuation of therapy.^{13,114} Age (>70 years) and histologic type of DLBCL are associated with shorter survival.¹¹⁴ In patients with DLBCL, clonality of the immunoglobulin heavy chain is associated with a decreased disease-free survival.¹¹⁴

HIV-related lymphomas

Key point

- **Patients with HIV can develop several Epstein–Barr virus–associated lymphoproliferative disorders, including primary central nervous system lymphoma, primary effusion lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, plasmablastic lymphoma, and Hodgkin lymphoma**

Patients with HIV are more susceptible to developing lymphoma, particularly in the central nervous system, which often displays a similar phenotype to posttransplant lymphoma.⁸ EBV can be detected in approximately 60% of HIV-related lymphomas, and nearly all cases of primary central nervous system lymphoma are associated with EBV.^{4,15} Several types of lymphoma that have been connected to EBV infection in HIV patients, including primary central nervous system lymphoma, primary effusion lymphoma, BL, DLBCL, HL, and plasmablastic lymphoma (PL). Of note, while PL may be seen primarily in patients with HIV, it has also been reported to occur the elderly.¹¹⁵

HEMOPHAGOCYTIC SYNDROME

Key points

- **Hemophagocytic syndrome is a rapidly progressive histiocytosis**
- **Cutaneous involvement presents as purpuric macules, papules, nonspecific generalized macular rash, or erythroderma**

- **Hemophagocytic syndrome may be precipitated by viral, bacterial, mycobacterial, fungal, or parasitic infections**
- **Epstein–Barr virus is the most commonly implicated infectious agent in hemophagocytic syndrome**

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis or macrophage activation syndrome, is a rare but potentially fatal, rapidly progressive histiocytosis that is characterized by impaired function of NK cells and cytotoxic T cells.¹¹⁶ Deficient cytolytic activity results in lymphocyte activation, cytokine overproduction, the proliferation of benign macrophages, and, eventually, hemophagocytosis.¹¹⁷⁻¹¹⁹ It can occur in the setting of chronic active EBV infection, as discussed in part I of this continuing medical education article. Clinically, HPS presents with a combination of systemic symptoms, including fever, hepatosplenomegaly, liver dysfunction, hypertriglyceridemia, hyperferritinemia, coagulation abnormalities, and pancytopenia.^{117,118} Children and immunosuppressed adults may be affected. Cutaneous involvement is uncommon and often nonspecific, presenting as purpuric macules, papules, a transient, generalized macular rash, or erythroderma.¹¹⁶

HPS is subdivided into 2 categories: primary/genetic and secondary/reactive HPS. Primary/genetic HPS is autosomal recessive and has been associated with mutations in the genes encoding perforin, Munc 13-4, and syntaxin 11 (PRF, UNC13S, and STX11, respectively).¹¹⁷⁻¹²⁰ In both primary/genetic and secondary/reactive HPS, T-cell activation can be precipitated by viral, bacterial, mycobacterial, fungal, or parasitic infections.¹¹⁷ EBV is the most commonly implicated infectious agent in HPS, as revealed by serology, molecular studies, and immunohistochemistry.^{119,121,122} EBV-associated HPS is more commonly seen in children and adolescents in Asia, and may appear during primary EBV infection or after reactivation.¹²³ Other infectious agents implicated in the pathogenesis of HPS include cytomegalovirus, HHV-8, HIV, influenza, parvovirus B19, enterovirus, adenovirus, paramyxovirus, rubella virus, human parainfluenza virus, flavivirus, hantavirus, *Mycobacterium tuberculosis*, *Brucella melitensis*, *Rickettsia*, *Acinetobacter baumannii*, Leishmania, malaria, Candida, Cryptococcus, Pneumocystis, Histoplasma, Aspergillus, Fusarium and Penicillium.¹¹⁷

The diagnosis of HPS relies heavily upon clinicopathologic correlation.¹¹⁶ Hemophagocytosis usually presents in the bone marrow, lymph nodes,

and spleen, but may be seen in any organ. Microscopic evaluation reveals well-differentiated activated macrophages with engulfed lymphocytes, erythrocytes, and platelets.¹¹⁷ Repeat biopsy specimens may need to be obtained if the initial biopsy specimen is negative.

Treatment for HPS includes cyclosporine, systemic steroids, intravenous immunoglobulin, chemotherapy, and stem cell transplantation.^{116,120} HPS follows a rapidly progressive clinical course, and is often fatal despite treatment because of bone marrow involvement and sepsis.¹¹⁸

ASSOCIATED SOLID TUMORS

Key point

- **Epstein–Barr virus has been associated with several malignancies, including nasopharyngeal carcinoma, gastric carcinoma, and leiomyosarcoma**

Nasopharyngeal carcinoma

Worldwide, nasopharyngeal carcinoma is a rare entity; however, it is endemic in southeast Asia and southern China.^{124,125} The presenting symptom is often a palpable lump in the neck.¹²⁶ The diagnostic workup includes an endoscopic biopsy and magnetic resonance imaging scan.¹²⁷ EBV is a well-known risk factor for the development of nasopharyngeal carcinoma, and tumor cells have been shown to express EBER and LMP1.¹²⁵ Although nonspecific, EBV serology (ie, the quantitative measurement of immunoglobulin A to VCA and early antigen) is used as a screening test for nasopharyngeal carcinoma; antibody titers remain elevated, even in disease remission.^{124,127} In contrast, real-time PCR is sensitive and specific, and has been shown to correlate well with tumor burden.^{124,127} In a metaanalysis performed by Zhao et al,¹²⁸ LMP1 expression was found to correlate with an increased risk of metastasis.

Gastric carcinoma

EBV-associated gastric carcinoma is a nonendemic neoplasm that occurs worldwide. Shibata and Weiss¹²⁹ detected EBV in 16% of gastric carcinomas, whether primary or metastatic disease, in North America.

Leiomyosarcoma

EBV-associated smooth muscle tumors are rare and occur primarily in immunocompromised children, including transplant patients, children with congenital immunodeficiencies, and those infected with HIV.^{130,131} They are often multifocal and arise in the gastrointestinal tract, lung, central nervous system,

and numerous other locations.^{130–134} Cutaneous manifestations are extremely uncommon. Ramdial et al¹³² reported 2 cases of cutaneous leiomyosarcoma arising in the dermis, and Tetzlaff et al¹³¹ reported a cutaneous leiomyosarcoma occurring on the abdomen; all 3 cases occurred in HIV-infected children.^{131,132} In all cases, EBV was found in tumors using EBER ISH.^{132–134} Surgical excision is the mainstay of treatment.^{130,132,133}

CONCLUSION

EBV infection has been associated and/or implicated in a host of lymphoproliferative disorders and other malignancies in both immunocompetent and immunosuppressed patients. While the precise nature of the relationship of the virus to the host regarding the pathogenesis of malignancy remains to be determined, identifying and recognizing the association is of importance. It is hoped that additional research in understanding the exact pathomechanism(s) of EBV-related oncogenesis will allow for the development of novel therapeutic approaches for these diseases.

REFERENCES

1. Bachmeyer C, Bazarbachi A, Rio B, et al. Specific cutaneous involvement indicating relapse of Burkitt's lymphoma. *Am J Hematol.* 1997;54:176.
2. Jacobson MA, Hutcheson ACS, Hurray DH, Metcalf JS, Thiers B. Cutaneous involvement by Burkitt lymphoma. *J Am Acad Dermatol.* 2006;54:1111–1113.
3. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. *Lancet.* 2012;379:1234–1244.
4. Grywalska E, Markowicz J, Grabarczyk P, Pasierski M, Roliński J. Epstein-Barr virus-associated lymphoproliferative disorders. *Postepy Hig Med Dosw (Online).* 2013;67:481–490.
5. Henle W, Henle G. Evidence for a relation of Epstein-Barr virus to Burkitt's lymphoma and nasopharyngeal lymphoma. *Bibl Haematol.* 1970;36:706–713.
6. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis. *Microbiology.* 1968;59:94–101.
7. De-The G, Geser A, Day NE, et al. Epidemiological evidence for causal relationship between Epstein-Barr virus and Burkitt's lymphoma from Ugandan prospective study. *Nature.* 1978;274:756–761.
8. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. *Nat Rev Cancer.* 2004;4:757–768.
9. Moormann AM, Snider CJ, Chelimo K. The company malaria keeps: how co-infection with Epstein-Barr virus leads to endemic Burkitt lymphoma. *Curr Opin Infect Dis.* 2011;24:435–441.
10. Cheyne A, Donati D, Orem J, et al. Endemic Burkitt's lymphoma as a polymicrobial disease: new insights on the interaction between *Plasmodium falciparum* and Epstein-Barr virus. *Semin Cancer Biol.* 2009;19:411–420.
11. Johnston WT, Mutualima N, Sun D, et al. Relationship between *Plasmodium falciparum* malaria prevalence, genetic diversity and endemic Burkitt lymphoma in Malawi. *Sci Rep.* 2014;4:3741.
12. Leoncini L, Raphael M, Stein H, Harris NL, Jaffe ES, Kluin PM. Burkitt lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, editors. *WHO classification of tumours of haematopoietic*

- and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 262-264.
13. Fernandez-Flores A. Epstein-Barr virus in cutaneous pathology. *Am J Dermatopathol.* 2013;35:763-786.
 14. Myers JL, Kurtin PJ, Katzenstein AL, et al. Lymphomatoid granulomatosis. Evidence of immunophenotypic diversity and relationship to Epstein-Barr virus infection. *Am J Surg Pathol.* 1995;19:1300-1312.
 15. Heslop HE. Biology and treatment of Epstein-Barr virus-associated non-Hodgkin lymphomas. *Hematology Am Soc Hematol Educ Program.* 2005;260-266.
 16. Pittaluga S, Wilson WH, Jaffe ES. Lymphomatoid granulomatosis. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 247-249.
 17. J1 Cohen, Kimura H, Nakamura S, Ko YH, Jaffe ES. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8-9 September 2008. *Ann Oncol.* 2009;20:1472-1482.
 18. Yazdi AS, Metzler G, Weyrauch S, et al. Lymphomatoid granulomatosis induced by imatinib-treatment. *Arch Dermatol.* 2007;143:1222-1223.
 19. McNiff JM, Cooper D, Howe G, et al. Lymphomatoid granulomatosis of the skin and lung. An angiocentric T-cell-rich B-cell lymphoproliferative disorder. *Arch Dermatol.* 1996;132:1464-1470.
 20. Roschewski M, Wilson WH. Lymphomatoid granulomatosis. *Cancer J.* 2012;18:469-474.
 21. Imaoka K, Furumura M, Maruyama R, Nagasako R, Morita E. Erythrodermic lymphomatoid granulomatosis: a case report. *Case Rep Dermatol.* 2011;3:244-250.
 22. Tong MM, Cooke B, Barnetson RS. Lymphomatoid granulomatosis. *J Am Acad Dermatol.* 1992;27:872-876.
 23. Camisa C. Lymphomatoid granulomatosis: two cases with skin involvement. *J Am Acad Dermatol.* 1989;20:571-578.
 24. Katzenstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. *Am J Surg Pathol.* 2010;34:e35-e48.
 25. Beatty MW, Toro J, Sorbara L, et al. Cutaneous lymphomatoid granulomatosis: correlation of clinical and biologic features. *Am J Surg Pathol.* 2001;25:1111-1120.
 26. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. *Clin Cancer Res.* 2007;13:5124-5132.
 27. Menon MP, Pittaluga S, Jaffe ES. The histological and biological spectrum of diffuse large B-cell lymphoma in the World Health Organization classification. *Cancer J.* 2012;18:411-420.
 28. Nakamura S, Jaffe ES, Swerdlow SH. EBV positive diffuse large B-cell lymphoma of the elderly. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 243-244.
 29. Oyama T, Ichimura K, Suzuki R, et al. Senile EBV+ B-cell lymphoproliferative disorders: a clinicopathologic study of 22 patients. *Am J Surg Pathol.* 2003;27:16-26.
 30. Ok CY, Papathomas TG, Medeiros LJ, Young KH. EBV-positive diffuse large B-cell lymphoma of the elderly. *Blood.* 2013;122:328-340.
 31. Martin B, Whittaker S, Morris S, Robson A. A case of primary cutaneous senile EBV-related diffuse large B-cell lymphoma. *Am J Dermatopathol.* 2010;32:190-193.
 32. Tokuda Y, Fukushima M, Nakazawa K, et al. A case of primary Epstein-Barr virus-associated cutaneous diffuse large B-cell lymphoma unassociated with iatrogenic or endogenous immune dysregulation. *J Cutan Pathol.* 2008;35:666-671.
 33. Castillo JJ, Beltran BE, Miranda RN, Paydas S, Winer ES, Butera JN. Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: what we know so far. *Oncologist.* 2011;16:87-96.
 34. Shimoyama Y, Oyama T, Asano N, et al. Senile Epstein-Barr virus-associated B-cell lymphoproliferative disorders: a mini review. *J Clin Exp Hematop.* 2006;46:1-4.
 35. Park S, Lee J, Ko YH, et al. The impact of Epstein-Barr virus status on clinical outcome in diffuse large B-cell lymphoma. *Blood.* 2007;110:972-978.
 36. Dojcinov SD, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer—a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol.* 2010;34:405-417.
 37. Dojcinov SD, Venkataraman G, Pittaluga S, et al. Age-related EBV-associated lymphoproliferative disorders in the Western population: a spectrum of reactive lymphoid hyperplasia and lymphoma. *Blood.* 2011;117:4726-4735.
 38. Li S, Feng X, Li T, et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. *Am J Surg Pathol.* 2013;37:14-23.
 39. Magro CM, Porcu P, Schaefer J, et al. Cutaneous CD4+ CD56+ hematologic malignancies. *J Am Acad Dermatol.* 2010;63:292-308.
 40. Kinney MC, Jones D. Cutaneous T-cell and NK-cell lymphomas: the WHO-EORTC classification and the increasing recognition of specialized tumor types. *Am J Clin Pathol.* 2007;127:670-686.
 41. Berti E, Recalcati S, Girelli V, Fanoni D, Venegoni L, Vezzoli P. Cutaneous extranodal NK/T-cell lymphoma: a clinicopathologic study of 5 patients with array-based comparative genomic hybridization. *Blood.* 2010;116:165-170.
 42. Choi YL, Park JH, Namkung JH, et al. Extranodal NK/T-cell lymphoma with cutaneous involvement: 'nasal' vs. 'nasal-type' subgroups—a retrospective study of 18 patients. *Br J Dermatol.* 2009;160:333-337.
 43. Yu JB, Zuo Z, Tang Y, et al. Extranodal nasal-type natural killer/T-cell lymphoma of the skin: a clinicopathologic study of 16 cases in China. *Hum Pathol.* 2009;40:807-816.
 44. Aozasa K, Takakuwa T, Hongyo T, Yang WI. Nasal NK/T-cell lymphoma: epidemiology and pathogenesis. *Int J Hematol.* 2008;87:110-117.
 45. Ahn HK, Suh C, Chuang SS, et al. Extranodal natural killer/T-cell lymphoma from skin or soft tissue: suggestion of treatment from multinational retrospective analysis. *Ann Oncol.* 2012;23:2703-2707.
 46. Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh SC. Extranodal NK/T-cell lymphoma, nasal type. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 285-288.
 47. Kato N, Aikawa K. Nasal type natural killer/T-cell lymphoma with subcutaneous panniculitis-like involvement: association with a poor prognosis. *J Am Acad Dermatol.* 2003;49:e4.
 48. Pincus LB, Zehnder JL, Neuhaus IM, Andreadis C, McCalmont TH. Presentation of extranodal natural killer T-cell lymphoma, nasal type, with poorly circumscribed erythematous patches. *J Clin Oncol.* 2010;28:e94-e95.
 49. Agarwal P, Ruzinova MB, Harris MH, Qureshi AA, Stebbins WG. Extranodal natural killer cell/t-cell lymphoma, nasal type, presenting as cutaneous nodules and a small-bowel perforation. *Am J Dermatopathol.* 2010;32:83-85.

50. Charli-Joseph Y, Saeb-Lima M, Hernández-Salazar A, Domínguez-Cherit J. Nasal-type extranodal natural killer/T-cell lymphoma presenting as genital ulcers. *J Am Acad Dermatol.* 2012;67:e157-e159.
51. Harabuchi Y, Yamanaka N, Kataura A, et al. Epstein-Barr virus in nasal T-cell lymphomas in patients with lethal midline granuloma. *Lancet.* 1990;335:128-130.
52. Au WY, Pang A, Choy C, Chim CS, Kwong YL. Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. *Blood.* 2004;104:243-249.
53. Au WY, Weisenburger DD, Intragumtornchai T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. *Blood.* 2009;113:3931-3937.
54. Qi SN, Li YX, Wang WH, et al. The extent of cutaneous lesions predicts outcome in extranodal nasal-type natural killer/T-cell lymphoma of the upper aerodigestive tract with secondary cutaneous involvement. *Leuk Lymphoma.* 2012;53:855-861.
55. Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol.* 2004;15:1097-1108.
56. Quintanilla-Martinez L, Ridaura C, Nagl F, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood.* 2013;122:3101-3110.
57. Quinlanilla-Martinez L, Kimura H, Jaffe ES. EBV-positive T-cell lymphoproliferative disorders of childhood. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 285-288.
58. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. *Pediatr Dermatol.* 2010;27:463-469.
59. Magaña M, Sangüesa P, Gil-Beristain J, et al. Angiocentric cutaneous T-cell lymphoma of childhood (hydroa-like lymphoma): a distinctive type of cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 1998;38:574-579.
60. Wang M, Wang S, Yang QP, et al. Hydroa vacciniforme-like lymphoma of an adult: a case report with review of the literature. *Diagn Pathol.* 2013;8:72.
61. Rodríguez-Pinilla SM, Barrios C, García J, et al. EBV-associated cutaneous NK/T-cell lymphoma: review of a series of 14 cases from Peru in children and young adults. *Am J Surg Pathol.* 2010;34:1773-1782.
62. Barrios C, Anderson VM, Zevallos-Giampietri E, et al. Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. *Appl Immunohistochem Mol Morphol.* 2002;10:7-14.
63. Iwatsuki K, Satoh M, Yamamoto T, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol.* 2006;142:587-595.
64. Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol.* 2001;45:569-578.
65. Doeden K, Molina-Kirsch H, Perez E, Warnke R, Sundram U. Hydroa-like lymphoma with CD56 expression. *J Cutan Pathol.* 2008;35:488-494.
66. Kimura H, Ito Y, Kawabe S, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. *Blood.* 2012;119:673-686.
67. Dogan A, Gaulard P, Jaffe ES, Ralfkiaer E. Muller-Hermelink. Angioimmunoblastic T-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 309-311.
68. Balarajan B, Conley JA, Scheinbein DM. Evaluation of cutaneous angioimmunoblastic T-cell lymphoma. *J Am Acad Dermatol.* 2011;65:855-862.
69. Brown HA, Macon WR, Kurtin PJ, Gibson LE. Cutaneous involvement by angioimmunoblastic T-cell lymphoma with remarkable heterogeneous Epstein-Barr virus expression. *J Cutan Pathol.* 2001;28:432-438.
70. Mahendran R, Grant JW, Hoggarth CE, Burrows NP. Angioimmunoblastic T-cell lymphoma with cutaneous involvement. *J Eur Acad Dermatol Venereol.* 2001;15:589-590.
71. Martin JE, Wagner AJ, Murphy GF, Pinkus GS, Wang LC. Granuloma annulare heralding angioimmunoblastic T-cell lymphoma in a patient with a history of Epstein-Barr virus-associated B-cell lymphoma. *J Clin Oncol.* 2009;27:e168-e171.
72. Weiss LM, Jaffe ES, Liu XF, Chen YY, Shibata D, Medeiros LJ. Detection and localization of Epstein-Barr viral genomes in angioimmunoblastic lymphadenopathy and angioimmunoblastic lymphadenopathy-like lymphoma. *Blood.* 1992;79:1789-1795.
73. Zhou Y, Attygalle AD, Chuang SS, et al. Angioimmunoblastic T-cell lymphoma: histological progression associates with EBV and HHV6B viral load. *Br J Haematol.* 2007;138:44-53.
74. Kawano R, Ohshima K, Wakamatsu S, Suzumiya J, Kikuchi M, Tamura K. Epstein-Barr virus genome level, T-cell clonality and the prognosis of angioimmunoblastic T-cell lymphoma. *Haematologica.* 2005;90:1192-1196.
75. Vrsalovic MM, Korac P, Dominis M, Ostojevic S, Mannhalter C, Kusec R. T- and B-cell clonality and frequency of human herpes viruses-6, -8 and Epstein Barr virus in angioimmunoblastic T-cell lymphoma. *Hematol Oncol.* 2004;22:169-177.
76. Ponciano A, de Muret A, Machet L, et al. Epidermotropic secondary cutaneous involvement by relapsed angioimmunoblastic T-cell lymphoma mimicking mycosis fungoides: a case report. *J Cutan Pathol.* 2012;39:1119-1124.
77. Lee Y, Lee KW, Kim JH, et al. Epstein-Barr virus-positivity in tumor has no correlation with the clinical outcomes of patients with angioimmunoblastic T-cell lymphoma. *Korean J Intern Med.* 2008;23:30-36.
78. Battegay M, Berger C, Rochlitz C, et al. Epstein-Barr virus load correlating with clinical manifestation and treatment response in a patient with angioimmunoblastic T-cell lymphoma. *Antivir Ther.* 2004;9:453-459.
79. Rüdiger T, Weisenburger DD, Anderson JR, et al. Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol.* 2002;13:140-149.
80. Soylu S, Güll U, Kılıç A, Heper AO, Kuzu I, Minareci BG. A case with an indolent course of subcutaneous panniculitis-like T-cell lymphoma demonstrating Epstein-Barr virus positivity and simulating dermatitis artefacta. *Am J Clin Dermatol.* 2010;11:147-150.
81. Kong YY, Dai B, Kong JC, et al. Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathologic, immunophenotypic, and molecular study of 22 Asian cases according to

- WHO-EORTC classification. *Am J Surg Pathol.* 2008;32:1495-1502.
82. Go RS, Wester SM. Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. *Cancer.* 2004;101:1404-1413.
 83. Nemoto Y, Taniguchi A, Kamioka M, et al. Epstein-Barr virus-infected subcutaneous panniculitis-like T-cell lymphoma associated with methotrexate treatment. *Int J Hematol.* 2010;92:364-368.
 84. Jaffe ES, Gaulard P, Ralfkiaer E, Cerroni L, Meijer CJLM. Subcutaneous panniculitis-like T-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008. pp. 294-295.
 85. Willemze R, Jansen PM, Cerroni L, et al. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood.* 2008;111:838-845.
 86. Lee PY, Charley M, Tharp M, Jegesothy BV, Deng JS. Possible role of Epstein-Barr virus infection in cutaneous T-cell lymphomas. *J Invest Dermatol.* 1990;95:309-312.
 87. Jumbou O, Mollat C, N'Guyen JM, Billaudel S, Litoux P, Dréno B. Increased anti-Epstein-Barr virus antibodies in epidermotropic cutaneous T-cell lymphoma: a study of 64 patients. *Br J Dermatol.* 1997;136:212-216.
 88. Shimakage M, Sasagawa T, Kawahara K, Yutsudo M, Kusuoka H, Kozuka T. Expression of Epstein-Barr virus in cutaneous T-cell lymphoma including mycosis fungoïdes. *Int J Cancer.* 2001;92:226-231.
 89. Suzushima H, Asou N, Fujimoto T, et al. Lack of the expression of EBNA-2 and LMP-1 in T-cell neoplasms possessing Epstein-Barr virus. *Blood.* 1995;85:480-486.
 90. Kanavaros P, Ioannidou D, Tzardi M, et al. Mycosis fungoïdes: expression of C-myc p62/p53, bcl-2 and PCNA proteins and absence of association with Epstein-Barr virus. *Pathol Res Pract.* 1994;190:767-774.
 91. Angel CA, Slater DN, Royds JA, Nelson SN, Bleehen SS. Absence of Epstein-Barr viral encoded RNA (EBER) in primary cutaneous t-cell lymphoma. *J Pathol.* 1996;178:173-175.
 92. Fraga M, Forteza J. Diagnosis of Hodgkin's disease: an update on histopathological and immunophenotypical features. *Histol Histopathol.* 2007;22:923-935.
 93. Tanese K, Haratoh R, Yamamoto K, Wakabayashi A, Irie R, Miyakawa S. Epstein-Barr virus-positive Hodgkin lymphoma-like earlobe lymphoid infiltrate: case report. *Am J Dermatopathol.* 2009;31:838-845.
 94. Sioutos N, Kerl H, Murphy SB, Kadin ME. Primary cutaneous Hodgkin's disease. Unique clinical, morphologic, and immunophenotypic findings. *Am J Dermatopathol.* 1994;16:2-8.
 95. Landgren O, Caporaso NE. New aspects in descriptive, etiologic, and molecular epidemiology of Hodgkin's lymphoma. *Hematol Oncol Clin North Am.* 2007;21:825-840.
 96. Pallesen G, Sandvej K, Hamilton-Dutoit SJ, Rowe M, Young LS. Activation of Epstein-Barr virus replication in Hodgkin and Reed-Sternberg cells. *Blood.* 1991;78:1162-1165.
 97. Mueller N, Evans A, Harris NL, et al. Hodgkin's disease and Epstein-Barr virus. Altered antibody pattern before diagnosis. *N Engl J Med.* 1989;320:689-695.
 98. Weiss LM, Strickler JG, Warnke RA, Purtillo DT, Sklar J. Epstein-Barr viral DNA in tissues of Hodgkin's disease. *Am J Pathol.* 1987;129:86-91.
 99. Glaser SL, Lin RJ, Stewart SL, et al. Epstein-Barr virus-associated Hodgkin's disease: epidemiologic characteristics in international data. *Int J Cancer.* 1997;70:375-382.
 100. Levine PH, Ablashi DV, Berard CW, Carbone PP, Waggoner DE, Malan L. Elevated antibody titers to Epstein-Barr virus in Hodgkin's disease. *Cancer.* 1971;27:416-421.
 101. Goldman JM, Aisenberg AC. Incidence of antibody to EB virus, herpes simplex, and cytomegalovirus in Hodgkin's disease. *Cancer.* 1970;26:327-331.
 102. Surveillance, Epidemiology, and End Results Program website. SEER Data (1973-2010). 1973-2010 data (Nov 2012 submission). Available at: www.seer.cancer.gov. Accessed May 9, 2014.
 103. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients—BCSH and BTS Guidelines. *Br J Haematol.* 2010;149:675-692.
 104. Allen UD, Preiksaitis JK. AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant.* 2013;14:107-120.
 105. Sanae T, Daisuke W, Kazuhisa M, et al. Epstein-Barr virus-associated lymphoproliferative disorder presenting with skin involvement after CD34-selected autologous peripheral blood stem cell transplantation. *Eur J Dermatol.* 2007;17:242-244.
 106. Ward HA, Russo GG, McBurney E, Millikan LE, Boh EE. Posttransplant primary cutaneous T-cell lymphoma. *J Am Acad Dermatol.* 2001;44:675-680.
 107. Boubenider S, Hiesse C, Goupy C, Kriaa F, Marchand S, Charpentier D. Incidence and consequences of post-transplantation lymphoproliferative disorders. *J Nephrol.* 1997;10:136-145.
 108. Al-Mansour Z, Nelson BP, Evens AM. Post-transplant lymphoproliferative disease (PTLD): risk factors, diagnosis, and current treatment strategies. *Curr Hematol Malig Rep.* 2013;8:173-183.
 109. Smith JM, Rudser K, Gillen D, et al. Risk of lymphoma after renal transplantation varies with time: an analysis of the United States Renal Data System. *Transplantation.* 2006;81:175-180.
 110. Leblond V, Sutton J, Dorent R, et al. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. *J Clin Oncol.* 1995;13:961-968.
 111. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative report. *Am J Transplant.* 2004;2:222-230.
 112. Schumann KW, Oriba HA, Bergfeld WF, Hsi ED, Hollandswhirth K. Cutaneous presentation of posttransplant lymphoproliferative disorder. *J Am Acad Dermatol.* 2000;42:923-926.
 113. Naidu A, Kessler HP, Pavelka MA. Epstein-Barr virus-positive oral ulceration simulating Hodgkin lymphoma in a patient treated with methotrexate: case report and review of the literature. *J Oral Maxillofac Surg.* 2014;72:724-729.
 114. Ichikawa A, Arakawa F, Kiyasu J, et al. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: histology, Epstein-Barr virus, and clonality are important predictors of disease progression and regression. *Eur J Haematol.* 2013;91:20-28.
 115. Liu F, Asano N, Tatematsu A, et al. Plasmablastic lymphoma of the elderly: a clinicopathologic comparison with age-related Epstein-Barr virus-associated B cell lymphoproliferative disorder. *Histopathology.* 2012;61:1183-1197.
 116. Di Lernia V, Mansouri Y. Epstein-Barr virus and skin manifestations in childhood. *Int J Dermatol.* 2013;52:1177-1184.

117. Ansuni V, Rigante D, Esposito S. Debate around infection-dependent hemophagocytic syndrome in paediatrics. *BMC Infect Dis.* 2013;13:1-8.
118. Newman B, Hu W, Nigro K, Gilliam AC. Aggressive histiocytic disorders that can involve the skin. *J Am Acad Dermatol.* 2007;56:302-316.
119. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Gould C. Infections associated with hemophagocytic syndrome. *Lancet.* 2007;7:814-822.
120. Henter JI, Horne A, Aricó M, et al. Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48:124-131.
121. Kikuta H, Sakiyama Y, Matsumoto S, et al. Fatal Epstein-Barr virus-associated hemophagocytic syndrome. *Blood.* 1993;82: 3259-3264.
122. Sato S, Kawashima H, Oshiro H, et al. Virological and immunological characteristics of a 19-year-old Japanese female with fatal outcome with Epstein-Barr virus-associated hemophagocytic syndrome. *J Clin Virol.* 2004;31: 235-238.
123. Iwatsuki K, Yamamoto T, Tsuji K, et al. A spectrum of clinical manifestations by host immune responses against Epstein-Barr infections. *Acta Med Okayama.* 2004;58: 169-180.
124. Song C, Yang S. A meta-analysis on the EBV DNA and VCA-IgA in diagnosis of nasopharyngeal carcinoma. *Pak J Med Sci.* 2013;29:885-890.
125. Pathmanathan R, Prasad U, Chandrika G, Sadler R, Flynn K, Raab-Traub N. Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia. *Am J Pathol.* 1995;146: 1355-1367.
126. Colaco RJ, Betts G, Donne A, et al. Nasopharyngeal carcinoma: a retrospective review of demographics, treatment and patient outcome in a single centre. *Clin Oncol (R Coll Radiol).* 2013;25:171-177.
127. Chan AT. Nasopharyngeal carcinoma. *Ann Oncol.* 2010; 21(suppl 7):vii308-vii312.
128. Zhao Y, Wang Y, Zeng S, Hu X. LMP1 expression is positively associated with metastasis of nasopharyngeal carcinoma: evidence from a meta-analysis. *J Clin Pathol.* 2012;65:41-45.
129. Shibata D, Weiss LM. Epstein-Barr virus-associated gastric adenocarcinoma. *Am J Pathol.* 1992;140:769-774.
130. Jeribi A, Albano L, Berguignat M, et al. Epstein-Barr virus-associated hepatic leiomyosarcoma after renal transplantation: case report. *Transplant Proc.* 2010;42: 4356-4358.
131. Tetzlaff MT, Nosek C, Kovarik CL. Epstein-Barr virus-associated leiomyosarcoma with cutaneous involvement in an African child with human immunodeficiency virus: a case report and review of the literature. *J Cutan Pathol.* 2011;38: 731-739.
132. Ramdial PK, Sing Y, Deonarine J, Hadley GP, Singh B. Dermal Epstein Barr virus-associated leiomyosarcoma: tocsin of acquired immunodeficiency syndrome in two children. *Am J Dermatopathol.* 2011;33:392-396.
133. Sivendran S, Vidal CI, Barginear MF. Primary intracranial leiomyosarcoma in an HIV-infected patient. *Int J Clin Oncol.* 2011;16:63-66.
134. Suzuki K, Urushihara N, Fukumoto K, Watanabe K, Wada N, Takaba E. A case of Epstein-Barr virus-associated pulmonary leiomyosarcoma arising five yr after a pediatric renal transplant. *Pediatr Transplant.* 2011;15:E145-E148.

Cutaneous adverse effects of targeted therapies

Part I: Inhibitors of the cellular membrane

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Learning objectives

After completing this learning activity, participants should be able to identify the most common cutaneous adverse events associated with targeted therapies; describe the etiopathogenesis of cutaneous adverse effects associated with targeted therapies; and recognize clinical features of common cutaneous adverse effects associated with targeted therapies.

Disclosures

None declared.

There has been a rapid emergence of numerous targeted agents in the oncology community in the last decade. This exciting paradigm shift in drug development lends promise for the future of individualized medicine. Given the pace of development and clinical deployment of targeted agents with novel mechanisms of action, dermatology providers may not be familiar with the full spectrum of associated skin-related toxicities. Cutaneous adverse effects are among the most frequently observed toxicities with many targeted agents, and their intensity can be dose-limiting or lead to therapy discontinuation. In light of the often life-saving nature of emerging oncotherapeutics, it is critical that dermatologists both understand the mechanisms and recognize clinical signs and symptoms of such toxicities in order to provide effective clinical management. Part I of this continuing medical education article will review in detail the potential skin-related adverse sequelae, the frequency of occurrence, and the implications associated with on- and off-target cutaneous toxicities of inhibitors acting at the cell membrane level, chiefly inhibitors of epidermal growth factor receptor, KIT, and BCR-ABL, angiogenesis, and multikinase inhibitors. (J Am Acad Dermatol 2015;72:203-18.)

Key words: adverse sequelae; alopecia; antiangiogenic agents; anticancer; BCR-ABL; bevacizumab; cancer treatment; canertinib; cetuximab; chemotherapy; cutaneous adverse effects; dasatinib; dermatologic toxicities; disturbed wound healing; drug eruption; drug rash; drug reaction; dry skin; dual kinase inhibitors; epidermal growth factor receptor inhibitors; erbB receptor; erlotinib; gefitinib; genital rash; HER2; hyperkeratotic hand-foot skin reaction; imatinib; KIT; lapatinib; macular eruption; monoclonal antibodies; morbilliform; mucocutaneous hemorrhage; mucositis; multikinase inhibitors; nilotinib; panitumumab; papulopustular eruption; paronychia; pazopanib; platelet-derived growth factor receptor; photosensitivity; pigment changes; ranibizumab; side effects; small molecule; sorafenib; stomatitis; sunitinib; supportive oncodermatology; targeted therapy; toxic erythema; tyrosine kinase inhibitors; vandetanib; vascular endothelial growth factor; xerosis.

INTRODUCTION

Key points

- Targeted therapies offer more precise oncologic treatment options; however, they are not free of adverse effects

- Cutaneous adverse effects are among the most frequently encountered, and significantly impact both quality of life and health care economics

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Abbreviations used:

EGFR:	epidermal growth factor receptor
HhSP:	hedgehog signaling pathway
VEGFR:	vascular endothelial growth factor receptor

- **Dermatologists can provide key input in treatment of patients with targeted cancer therapies**

Virtually all cancers are driven by molecular aberrations that ultimately lead to uncontrolled proliferation. This notion has spurred the development of a spectrum of therapies specifically aimed at the molecular mechanisms contributing to cancer development and progression. The emergence of this class of agents, often referred to as “targeted therapies,” offers a promise of more effective treatments tailored to a specific disease and possibly even to an individual patient’s cancer.

Although designed to be significantly more “precise” than traditional chemotherapies, targeted therapies frequently induce adverse effects (AEs). Cutaneous toxicities are among the most frequently observed AEs¹ and, when severe or protracted, can result in significant morbidity, requiring dose modification or drug discontinuation.² The morbidity can affect patient’s quality of life, including patient’s physical,³ emotional,⁴ and psychological well-being.⁵ In addition, AEs can affect medication adherence, risk of infection, and cancer therapy dosing^{6,7} and result in a substantial economic burden⁵ and potentially time-exhaustive clinic visits for cancer patients. In one analysis, management of dermatologic toxicities of targeted therapies was estimated at a median of \$1920 per patient.⁸

Given the increasing use of targeted therapies, dermatology providers are encountering growing numbers of oncology patients who are experiencing cutaneous side effects of varied pathogeneses and complexity. The resulting need for a dual clinical expertise has led to collaborative efforts between dermatologists and oncologists, including the introduction of supportive oncodermatology fellowship programs.⁵ To allow for uniform reporting and proper cataloging of side effects between specialists caring for cancer patients, a standardized grading system has been established,⁹ and dermatologic AEs have been stratified accordingly.¹⁰

In this 2-part review, we address the key skin and skin appendage-related toxicities of the most prominent targeted anticancer therapies and discuss the incidence, pathogenesis, clinical presentations, and management strategies by drug

category (Table I). Part I will focus on inhibitors of membrane-associated therapeutic targets (Fig 1), while part II details inhibitors of intracellular signaling pathways and immunotherapies.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Key points

- **Epidermal growth factor receptor inhibitors generate a unique constellation of skin toxicities, including papulopustular eruption, hair and nail changes, mucositis, and photosensitivity**
- **The severity of papulopustular eruption directly correlates with epidermal growth factor receptor inhibitor efficacy and patient outcomes**
- **Prophylaxis and the early management of cutaneous toxicities may prevent dose reduction or dose discontinuation**

Epidermal growth factor receptor (EGFR) inhibitors are among the first families of targeted therapies and are used in the treatment of several malignancies, including colorectal, head and neck, non–small cell lung, and breast cancers.¹¹ This class of EGFR inhibitors includes monoclonal antibodies to EGFR (eg, cetuximab and panitumumab), small-molecule tyrosine kinase inhibitors specific for EGFR (eg, erlotinib and gefitinib), dual kinase inhibitors of EGFR and HER2 (ie, lapatinib, neratanib, and afatinib), inhibitors of erbB receptors (ie, canertinib), and other less specific multikinase inhibitors (eg, vandetanib). Most agents targeting EGFRs produce a similar spectrum of dermatologic toxicities,¹² as detailed below.

The unique constellation of class-specific cutaneous AEs associated with EGFR inhibition clearly point to the important role of EGFR in epidermal and pilosebaceous homeostasis.^{13–15} Indeed, EGFRs are abundantly expressed in the epidermis and its appendages,¹⁶ consistent with the high incidence of AEs induced by EGFR inhibition. Interestingly, EGFR has also been shown to play a putative role in restraining interleukin-1 (IL-1)-dependent inflammatory reactions at the hair follicle level, possibly shedding light on the acneiform papulopustular eruptions¹⁷ seen in conjunction with EGFR blockade. In addition to altering IL-1 and tumor necrosis factor–alpha,¹⁸ EGFR effects on IL-8 have more recently been implicated as a mechanism mediating EGFR-induced AEs.¹⁹ The observed skin toxicities are clearly related to EGFR itself, rather than off-target effects of EGFR inhibitors, because the reversal of EGFR inhibitor–induced receptor

Table I. Management of cutaneous adverse effects of targeted therapies

Targeted therapy class	Agents within class	Dermatologic toxicities	Management	Level of evidence
EGFR inhibitors	Monoclonal antibodies to EGFR: cetuximab and panitumumab	Papulopustular eruption	Preventative: low-potency topical steroids (class VII) and sunscreen; consider prophylactic systemic antibiotics (tetracyclines)	IB
	TKI specific for EGFR: erlotinib and gefitinib		Treatment: low-potency topical steroids (class VI/VII); clindamycin 1% topical	III
	Dual kinase inhibitors of EGFR and HER2: lapatinib			
	Inhibitors of erbB receptors: canertinib		Systemic antibiotics: tetracyclines	III
	Less specific multikinase inhibitors: vandetanib	Xerosis/fissures	Isotretinoin (20-30 mg/day)	III
			Bland emollient creams and keratolytics: urea, salicylic acid, lactic acid, and zinc oxide	IIB
			Medium- to high-potency topical steroids (class II-IV); liquid glues or cyanoacrylate	IIB
		Hair changes: kinking, trichomegaly, hirsutism, alopecia (pattern or cicatricial), or poliosis	Nonscarring hair loss: topical minoxidil	IB
			Scarring hair loss: topical steroids or antibiotic spray	III
			Hypertrichosis Regular eyelash trimming Eflornithine Laser hair reduction	III IV IB
KIT and BCR-ABL inhibitors	Imatinib, nilotinib, and dasatinib	Mucositis	Topical steroids Antiseptic washes Anesthetic rinses	IIB III III
			Antiseptic soaks	IB
			Topical steroids or calcineurin inhibitors	IB
	Nilotinib, dasatinib	Nail changes: paronychia, onycholysis, pyogenic granuloma-like lesions, or brittle nails	Systemic antimicrobials: tetracyclines or culture-driven	III/IB
			Biotin for brittle nails	IIB
Antiangiogenic agents	Selective VEGFR inhibitors: bevacizumab and ranibizumab	Photosensitivity	Strict sun precautions, including photoprotective clothing and the use of broad-spectrum sunscreens	III
		Edema	Limited sodium diet (2 g/day); diuretics if severe	III
		Morbilliform eruption	Topical steroids (class III/IV) or short course of oral steroids; treatment interruption if grade III/IV	III
		Pigmentary changes	Typically reversible with dose reduction/termination	III
		Mucocutaneous hemorrhage	Initiation or continuation of treatment is not recommended	IV
		Disturbed wound healing	Consider delaying start/restart of treatment until 28 days after surgery	III
			Discontinue treatment for all wound complications	III

Continued

Table I. Cont'd

Targeted therapy class	Agents within class	Dermatologic toxicities	Management	Level of evidence
	Nonselective antiangiogenesis multikinase agents: sorafenib, sunitinib, and pazopanib	Hyperkeratotic hand–foot skin reaction	Prevention: pretreatment evaluation with podiatrist, orthopedic shoe inserts Management Grade I: emollients and keratolytics Grade II: add topical steroids (class I/II) and topical anesthetics, nonsteroidal antiinflammatory drugs Grade III: add antiseptic soaks; treatment interruption	III
		Inflammatory eruptions	Topical steroids (class III/IV) or short course of systemic steroids	IV
		Hair changes: alopecia, kinking, and depigmentation	Generally reversible after treatment is stopped Concealment measures, minoxidil 5% foam, and frequent clipping	IIB
				IV

Level of evidence: IA evidence includes evidence from metaanalysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

EGFR, Epithelial growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

dephosphorylation with menadione (vitamin K₃) results in decreased keratinocyte toxicities.²⁰

Cutaneous AEs in patients who are taking EGFR inhibitors range in incidence from 50% to 90%²¹ and include a spectrum of toxicities. The most prevalent reactions are papulopustular eruption, xerosis, hair changes, mucositis, and paronychia.

Papulopustular eruption

The eruption of papules and pustules in a seborrheic distribution is the most common and earliest cutaneous side effect of anti-EGFR agents (Fig 2), occurring in a dose-dependent fashion in >75% of patients after 1 to 2 weeks of therapy.^{22,23} Although commonly described as acneiform,²⁴ the eruption lacks comedones and nodulocysts and, unlike acne, is commonly associated with pruritus.²⁵ Perhaps the best nomenclature is papulopustular eruption in a seborrheic distribution, to avoid connotation of an acne-like process—largely because the treatments differ.^{12,25}

The eruption consists of folliculocentric pruritic papules evolving into pustules that may coalesce into lakes of pus involving the head, neck, trunk, and proximal upper extremities. Rupture of these pustules may lead to crusting and hyperkeratosis (Fig 3). Grade severity is based on the body surface area (BSA) involved and degree of limitation in performing activities of daily living (ADL).¹⁰ Severe

eruption occurs in <10% of patients.^{23,26} The histopathologic results reveal aseptic suppurative folliculitis¹⁵; however, the epidermal disruption associated with evolving papules and pustules often leads to bacterial superinfection. While generally occurring within the first weeks of therapy, in a subset of patients the eruption can appear after ≥3 weeks of treatment.²⁷ Dose-escalation and reinitiation of therapy²⁴ have been reported to accentuate flares. Although photoexposure has been reported to aggravate the flares²⁸ (Fig 2), sunscreen use in a placebo controlled trial did not prevent or attenuate EGFR inhibitor-induced eruption.²⁹ Sites treated with previous radiation are typically spared,³⁰ likely because of radiation-induced adnexal unit drop-out. Although a history of seborrhea has not been linked to a greater risk of severe eruption,²⁴ there may be a common genetic predisposition to developing folliculitis and responding to EGFR-directed treatment.³¹ Durable postinflammatory hyperpigmentation can occur, especially in patients with darker skin.¹² An elevated plasma creatine kinase level has been linked to rash severity, and may have potential in predicting which patients develop severe eruptions.³²

Treatment of papulopustular eruption. Because the development of this eruption and its severity directly correlate with tumor response to EGFR blockade and overall survival,^{18,33} patients

MOLECULAR SIGNALING PATHWAYS

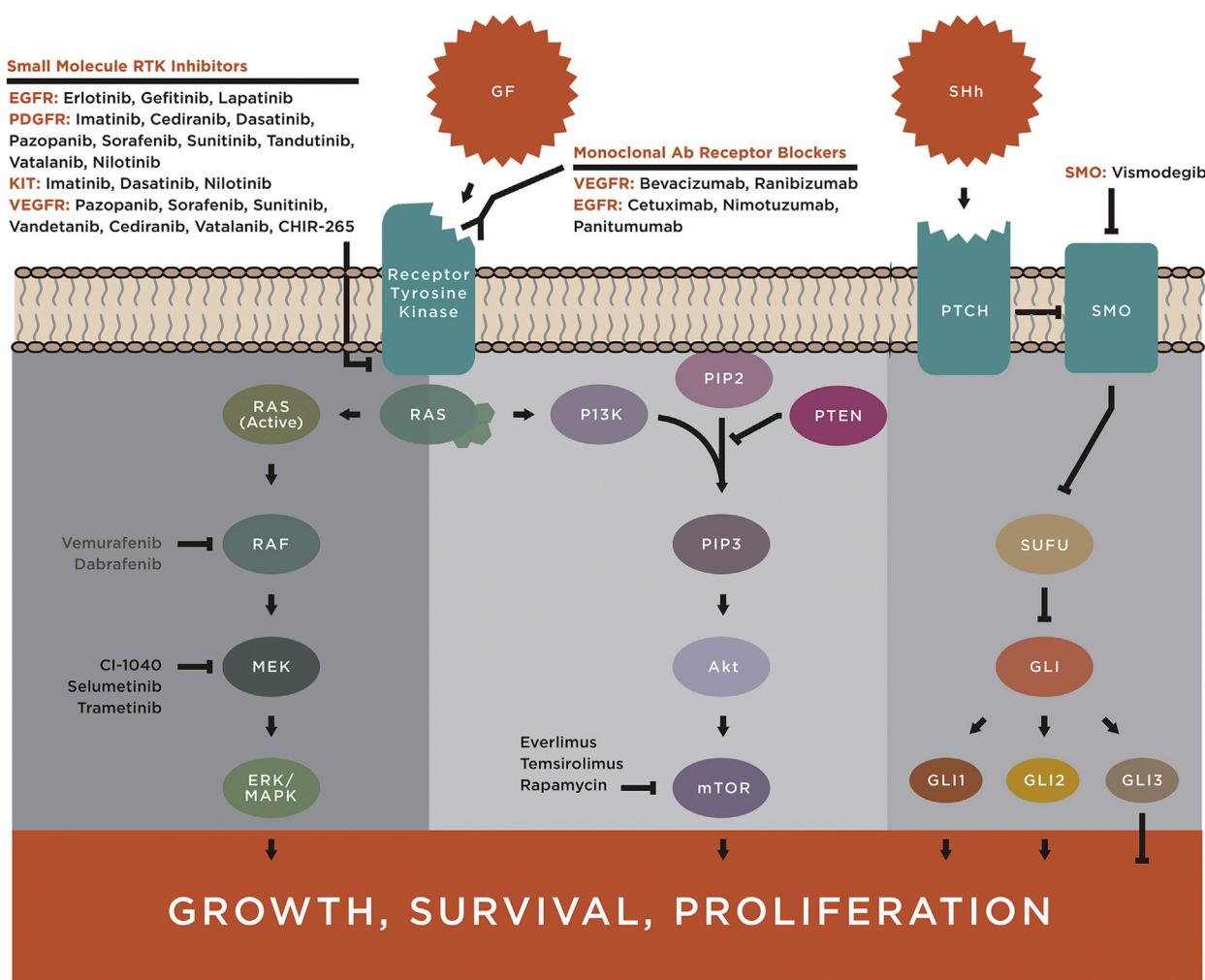


Fig 1. Molecular signaling pathways. Targeted agents listed are meant to be representative and are not intended to be all-inclusive for targeted agent families. *GF*, Growth factor; *RTK*, receptor tyrosine kinase; *SHh*, sonic hedgehog; *SMO*, smoothened.

should be counseled to expect some degree of inflammatory eruption. Management with topical and/or systemic modalities is based on the extent of the eruption and degree of patient discomfort. Sun protection may help, especially in patients with Fitzpatrick skin types I to III.²⁸ Hot water baths were reported to exacerbate the eruption and should be avoided.³⁴ Pruritus is a commonly associated component of the rash,³⁵ and can be alleviated with antihistamines (eg, cetirizine, loratadine, and hydroxyzine). When severe, the authors find titrating doses of doxepin most useful.

Grade 1 eruptions (<10% BSA with or without pruritus¹⁰) may be managed successfully with topical medications alone, including antibiotics, antiseptic

creams, and/or low potency topical corticosteroids,^{25,36} although the latter are typically reserved for use on the scalp because facial use may have untoward effects on the eruption.²⁵ Topical calcineurin inhibitors are helpful antiinflammatory agents,³⁷ yet their regular use is hampered by irritant potential, off-label use, and cost. Because the eruption lacks comedones, comedolytics, such as retinoids, are not indicated and can be irritating.³⁸ Menadione (vitamin K₃) may be a useful topical tool in the future²⁰ but is not yet commercially available. Nonacneogenic makeup may be recommended as a camouflage measure.

Grade 2 and 3 eruptions ($\geq 10\text{-}30\%$ BSA, tenderness, pruritus, and/or superinfection¹⁰) often require

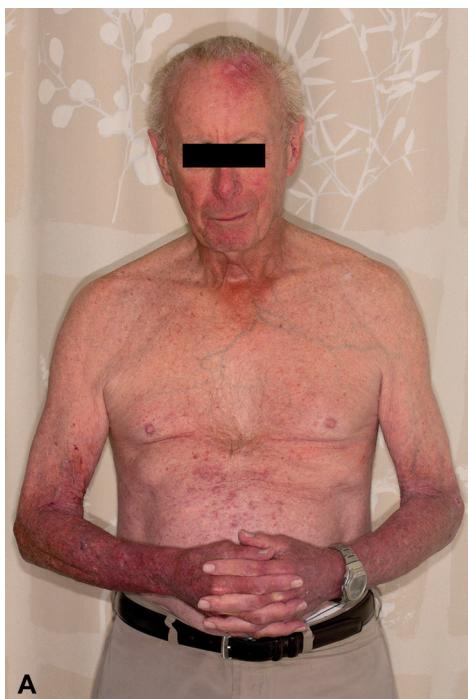
**A****B**

Fig 2. Papulopustular eruption associated with epithelial growth factor receptor inhibitors. **A**, Papules and pustules are present in a seborrheic and photoexposed distribution. **B**, High-power view of follicle-centered papules of the chest and abdomen.

systemic treatment. Tetracyclines are considered first-line agents and are likely active through their antiinflammatory properties.¹² Given the higher prevalence of bacterial superinfection with *Staphylococcus* species than in *acne vulgaris*,²⁴ cyclines likely also play an antimicrobial role. However, the prophylactic use of tetracyclines may not result in attenuation of eruption severity,³⁹ contrary to previous reports.^{38,40} Regional susceptibility patterns of *Staphylococcus* species may require use of penicillinase-resistant beta-lactam antibiotics. Isotretinoin, in low doses, has been shown to be effective.⁴¹⁻⁴³ The use of systemic steroids is generally avoided because they may induce a similar eruption.²⁵



Fig 3. Papulopustular eruption and alopecia associated with epithelial growth factor receptor inhibitors. Pustule rupture and subsequent crusting and hyperkeratosis occurring on the scalp associated with ivory white plaques of scarring alopecia.



Fig 4. Hair changes associated with epithelial growth factor receptor inhibitors. Note the acquired course texture and kinkiness of the scalp hair.

Xerosis

Approximately one-third of patients receiving EGFR inhibitors exhibit progressive xerosis in a dose-dependent fashion over weeks while on therapy²⁴; typically, the dryness is most pronounced along the extremities during months 1 to 3 of treatment. Increased skin fragility can occur leading to fissuring and easy bruising.⁴⁴ There may be significant pain because of fissuring and severe pruritus,³⁵ and secondary skin infection with *Staphylococcus aureus* or, rarely, herpes simplex virus can occur.²⁵



Fig 5. Trichomegaly associated with epithelial growth factor receptor inhibitors.



Fig 6. Paronychia associated with epithelial growth factor receptor inhibitors.

Treatment of xerosis. Patients are instructed to avoid dehydrating skin practices and skin care products (ie, bath foams, shower gels, harsh soaps, and very hot water). The early initiation of frequent moisturization with a thick, bland emollient can be preventative. Topical gels, if used in the initial treatment of a crusted papulopustular eruption, may ultimately potentiate xerosis^{45,46}—at which point vehicles should be changed to creams or ointments. Attention to the appropriate balance between occlusive ointments, which ameliorate dryness but may facilitate folliculitis and drying topical agents, which are soothing to acute inflammation yet exacerbate xerosis, must be kept in mind.⁴⁶ In light of recently elucidated mechanisms, the associated pruritus may be treated with antihistamines and, when severe, the neurokinin-1 receptor inhibitor aprepitant has been successful.^{47,48}

Hair changes

Changes in hair quality, texture, and growth pattern can be seen starting in the second or third month of treatment. The scalp hair grows more slowly, adopts a more fine and brittle quality, and becomes kinky⁴⁹ (Fig 4). Eyelash hair changes are characteristic and include hairs becoming long, rigid, and thicker (trichomegaly⁵⁰⁻⁵⁶; Fig 5). Inward lash curling may result in keratitis.⁵⁷ The eyebrows may

also thicken and develop hypertrichotic spread onto the periocular skin or glabella.⁵⁸ Women may experience hirsutism of the upper lip, whereas diminished need for shaving of the male beard may be noticed. Alopecia is mild and usually manifested in an androgenetic hair loss pattern²⁵; however, erlotinib-induced cicatricial alopecia and inflammatory nonscarring alopecia have been described^{59,60} (Fig 3). Poliosis has also been documented.⁵¹

Management of hair changes. Cutting of the eyelashes may be necessary to prevent keratitis. Frequent brushing helps loosen scalp hair kinkiness, making it easier to style and less brittle. Facial hypertrichosis tends to be readily reversible upon interruption of treatment; however, depilatory creams or laser epilation may speed clearance for those on long-term treatment.

Mucositis

The oral mucosa may develop aphthae, xerostoma, or geographic tongue.⁴⁴ Genital involvement is less common, manifesting as vulvovaginitis, balanitis, or genital aphthae. As noted, conjunctivitis and keratitis may occur.⁵⁷

Treatment of mucosal toxicities. Aphthae are managed in a similar fashion to idiopathic aphthosis with local therapies (ie, topical steroids, antiseptic washes, or anesthetics). Lubricants decrease discomfort of nasal or vaginal dryness. Lubricating eyedrops ameliorate most ocular symptoms associated with dryness. However, ophthalmologic consultation should be considered in cases of chronic corneal irritation to prevent ulceration or other serious ocular complications.⁵⁷

Nail changes

Nail toxicity is frequently encountered during treatment with EGFR inhibitors; all-grade nail toxicity occurred in 17.2% of patients in a recent metaanalysis.⁶¹ Nail changes can affect the entire nail unit, including the nail bed (onycholysis), nail fold (paronychia [Fig 6] and pyogenic granuloma-like

lesions), and nail matrix (dyspigmentation and brittle nails).^{27,62-65} Nail fold inflammation may progress to appear similar to pyogenic granuloma, particularly of the great toes; while initially sterile, superinfection with bacteria or fungi may occur. These changes can cause significant debilitation, necessitating dose adjustment or even temporary discontinuance of the targeted therapy.⁶²

Nail treatments. Treatment measures include wet dressings, cushioning inserts within shoes to pad the affected nails, topical or systemic antibiotics/antifungals, and pain control. Caution against ill-fitting shoes should be provided. Nail fold inflammation puts the nail unit at high risk of infection, and daily antiseptic soaks are a judicious measure, as is the early application of mild to medium potency topical corticosteroids when inflammation is noted.⁶⁶ Systemic antibiotics/antifungals may be considered when superinfection is detected; however, because infectious organisms are not the primary etiologic factor of EGFR inhibitor–induced paronychia, improvement may be modest.⁶² A recent report showed promise with the daily application of autologous platelet-rich plasma for paronychia.⁶⁷

Photosensitivity

Telangiectasia,²¹ hyperpigmentation,²¹ and photosensitive eruption²⁸ have been reported, supporting in vitro studies showing that ultraviolet radiation results in altered keratinocyte survival and proliferation in the setting of EGFR blockade.^{68,69}

Photosensitivity management. Hyperpigmentation gradually fades over months after treatment is discontinued. Bleaching agents and cosmetic camouflage may provide acceptable patient satisfaction. Dutiful sun precautions are prudent while taking EGFR inhibitors because photoexposure may exacerbate dermatologic toxicities.²⁸ Although telangiectasias gradually clear after treatment discontinuation, vascular light devices (ie, pulsed-dye laser or intense pulsed light therapy) or electrocoagulation may accelerate telangiectasia disappearance.

Long-term skin sequelae

The AEs that most commonly persist beyond 6 months of therapy are hair changes, pruritus, xerosis, and nail inflammation. Although most patients experience resolution of the papulopustular eruption, in some patients it may persist beyond 6 months.

Management. Long-term cutaneous toxicities may significantly alter a patient's quality of life⁷⁰ and may be dose-limiting. Close collaboration in a

multidisciplinary fashion, particularly between the treating oncologists and dermatologists, can promote successful long-term management and prevent dose decreases or drug discontinuation in most instances. Debilitating pruritus may be managed with aprepitant.^{27,35,47}

KIT AND BCR-ABL INHIBITORS

Key points

- Among the oldest targeted inhibitors, blocking agents of KIT and BCR-ABL have been described to cause a series of cutaneous toxicities, including a broad spectrum of inflammatory eruptions
- Most adverse effects in this class are dose-related and reversible after drug discontinuation

Imatinib, nilotinib, and dasatinib are inhibitors of tyrosine kinases generated from the *bcr-abl* fusion protein, c-Kit, and platelet-derived growth factor receptors (PDGFRs). The *bcr-abl* protein is the result of chromosome 9:22 translocation found in chronic myelogenous leukemia (CML), while the majority of gastrointestinal stromal tumors (GISTs) have a constitutively active c-Kit receptor. PDGFR kinases are involved in some types of hypereosinophilic syndrome and chronic myelomonocytic leukemia. In addition to the common use of KIT and *bcr-abl* inhibitors in these settings, efficacy of this class of agents was documented in dermatofibrosarcoma, systemic mastocytosis, AIDS-related Kaposi sarcoma, and KIT-mutated melanoma.^{6,71,72} Cutaneous AEs are the most frequent nonhematologic sequelae of this family and are generally not severe.

Edema

Facial edema, sometimes accompanied by severe weight gain,⁷³ may appear in the majority of patients⁷⁴⁻⁷⁶ in a dose-dependent fashion.⁷⁵ Modulation of interstitial fluid homeostasis from PDGFR inhibition is likely contributory to the fluid collection,⁷⁷ and diuretics may be required if severe.⁷⁸ Edema mimicking dermatomyositis has been described.⁷⁹

Morbilliform eruption

A majority of patients will develop a pruritic generalized morbilliform eruption that begins on average 9 weeks after treatment initiation.^{80,81} Rarely, the eruption may be severe (grade 3 or 4).⁸⁰ Female sex and imatinib were independent risk factors of a morbilliform eruption after multivariate analysis in 1 study.⁷⁵

Pigmentary changes

Dyspigmentation associated with imatinib use has been described in a localized, patchy, or diffuse distribution. This is consistent with the documented role of c-kit in the physiology of melanocytes, regulating melanogenesis, proliferation, migration, and survival.^{82,83} Patients with darker skin are generally more heavily affected.^{6,80} Hypopigmentation of the skin, which also may include the hair,^{84,85} is more common than increased pigment change.⁸⁶ Worsening of preexisting vitiligo has been described.⁸⁷ Onset is 4 weeks on average,⁷⁴ and the changes are generally reversible after discontinuation of the drug.⁷⁸

Other inflammatory eruptions

Reports have linked the new-onset or exacerbation of preexisting eruption of many inflammatory skin conditions to the use of imatinib, nilotinib, and dasatinib. These include lichenoid reactions,⁸⁸⁻⁹⁵ psoriasis,^{75,96,97} pityriasis rosea-like eruption,⁹⁸⁻¹⁰⁰ acute generalized exanthematous pustulosis,¹⁰¹⁻¹⁰³ DRESS syndrome,¹⁰⁴ Stevens-Johnson syndrome,^{73,105} urticaria,⁸⁶ acute neutrophilic dermatosis,¹⁰⁶⁻¹⁰⁸ photosensitivity,^{75,109} pseudolymphoma,¹¹⁰ porphyria cutanea tarda,^{111,112} small vessel vasculitis,¹¹³ panniculitis,^{75,113,114} perforating folliculitis,¹¹⁵ and erythroderma.¹¹⁶⁻¹²¹

Alopecia

Alopecia is listed in the package insert of nilotinib; however, the clinical and histologic features are incompletely described. One report noted generalized alopecia with histologic findings of a scarring process.¹²²

Treatment considerations. Cutaneous effects of this drug family are generally reversible, and local treatment measures can abate symptoms, preventing targeted treatment interruption. Severe or persistent dose-dependent manifestations may require a dose reduction or temporary stoppage.

ANTIANGIOGENESIS AGENTS

Key point

- The inhibition of angiogenesis also affects normal skin homeostasis, leading to mucocutaneous hemorrhage and poor wound healing

While endothelial cells in normal tissue are typically not mitotically active,¹²³ neoplastic tissue features high cellular turnover and rapid growth capacity. Neovascularization is an important element to maintaining oxygen supply to the rapidly proliferating neoplastic cells. More than 30 growth

factors involved in the promotion and inhibition of angiogenesis have been identified.¹²⁴ Vascular endothelial growth factor (VEGF) and the VEGF tyrosine kinase receptor system play an integral role in this process. Activin receptor-like kinase-1 (ALK1) has also emerged as a potential target in anti-angiogenesis treatment of cancer.¹²⁵ The selective blockade of VEGF using monoclonal antibodies has been available to oncologists since bevacizumab was approved by the US Food and Drug Administration in 2005. Along with ranibizumab, which was released in 2007, VEGF inhibitors are also used intravitreally for the treatment of macular degeneration.

VEGF inhibitors result in a decreased number of endothelial cells and the decreased formation of microcapillaries within tumor tissue. In addition, vascular permeability is impaired, thereby indirectly inhibiting tumor growth.¹²⁶ Because these mechanisms are also critical to maintaining normal tissue homeostasis, it is not unexpected that therapeutic VEGF inhibition would also be associated with untoward mucocutaneous side effects.

Mucocutaneous hemorrhage

Because of the effect of VEGF inhibitors on vascular permeability and proliferation, their use may result in mucosal bleeding and/or cutaneous hemorrhage.¹²⁷ Mild mucosal bleeding, most commonly manifesting as epistaxis, is seen in 20% to 40% of patients who are taking bevacizumab.¹²⁸ Initiation of VEGF inhibitor treatment is not recommended in the presence of skin and/or mucosal hemorrhage.

Disturbed wound healing

Inhibition of the VEGF pathway can disrupt wound repair and result in delayed wound healing in a dose-dependent fashion¹²⁸ and fistula formation.¹²⁹ This becomes a consideration for surgical planning in both the adjuvant and neoadjuvant settings.^{130,131}

MULTIKINASE INHIBITORS

Key points

- Multikinase inhibitors affect many tyrosine kinase systems and result in a vast array of skin-related adverse effects
- Hand-foot skin reaction is a poorly understood painful complication that often negatively affects drug dosing; treatments for hand-foot skin reaction are limited
- Inflammatory, appendageal, and neoplastic skin toxicities overlap with other drug categories

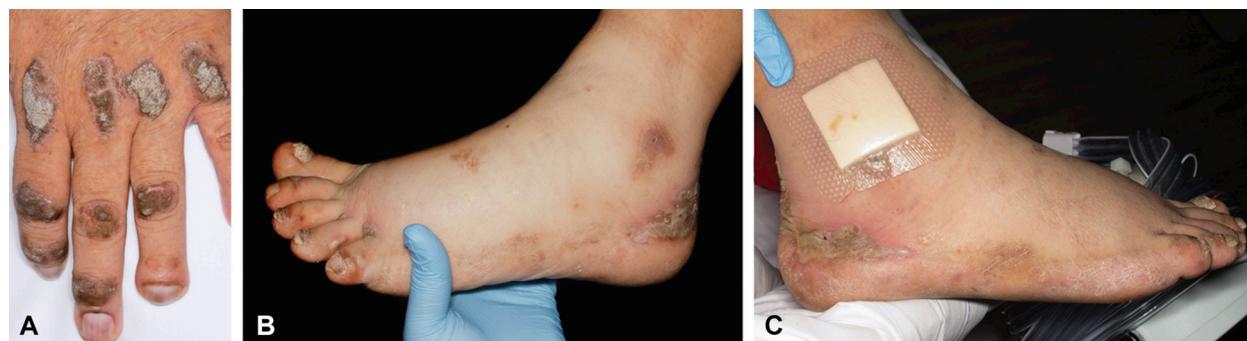


Fig 7. Hyperkeratotic hand–foot skin reaction of sorafenib. Hyperkeratotic plaques overlying points of pressure on the (A) hands and (B and C) feet.

Sorafenib, sunitinib, pazopanib, and vandetanib are small molecule inhibitors of the tyrosine kinase activity of the intracellular portion of the VEGF receptor. They also inhibit other tyrosine kinase receptors, such as PDGFR, EGFR, KIT, RET, Flt3, and RAF. As such, many of the cutaneous side effects observed with their use overlap with those described elsewhere of more target-specific therapies. Focus on the findings unique to these multikinase inhibitors will be made in this section, with only a brief mention of the overlapping features.

Hyperkeratotic hand–foot skin reaction

Hyperkeratotic hand–foot skin reaction (HFSR) is a painful complication seen most frequently during the early weeks of use with sorafenib (all grade, 10-63%; grade ≥ 3 , 2-36%),¹³²⁻¹³⁸ sunitinib (all grade, 10-28%; grade ≥ 3 , 4-12%),¹³⁹⁻¹⁴² and pazopanib (all grade, 11%; grade ≥ 3 , 2%).¹⁴³ Hyperkeratotic plaques develop predominantly over sites of pressure or friction (Fig 7, A and B). Plaques may have significant inflammation¹⁴⁴ and xerotic hyperkeratosis, often in a bilateral symmetric distribution,^{145,146} causing pain and debilitation that interfere with activities of daily living.¹⁴⁷ Sequential biopsy specimens reveal progressive accumulation of hyperkeratosis with focal parakeratosis.¹⁴⁸ HFSR does not appear to be related to increased excretion of the agent through sweat¹⁴⁹; rather, the pathogenesis is likely related to VEGF inhibition/vessel regression and negative effects on trauma-induced vascular repair capacities.¹⁵⁰

Management strategies. Patients should be informed of this dose-dependent reaction, and preventative measures should be instituted from the onset of treatment. Pretreatment evaluation with a podiatrist is useful to treat preexisting hyperkeratotic plaques and prescribe orthopedic soles along with wide, flexible shoes. Keratolytic

agents,¹⁵¹ pyridoxine,¹⁵² or systemic agents, such as retinoids,¹⁵³ have not been successful in preventing HFSR.

Should HFSR occur, treatment considerations¹² include the following: grade 1 (minimal skin changes without pain): emollients, keratolytic creams, and gel or foam-based shoe inserts—no dosage adjustment is typically needed; grade 2 (skin changes with pain limiting instrumental ADL): potent topical corticosteroids applied consecutively for 7 to 10 days in addition to treatment measures for grade 1 toxicity—targeted treatment dose reduction by 50% should be considered; and grade 3 (severe skin changes with debilitating pain limiting self-care ADL): in addition to treatment measures for grade 2 HFSR, patients should perform local antiseptic baths of blisters and erosions—targeted treatments should be interrupted for at least 1 week, and only resumed at a reduced dose after recovery of toxicity to grade 0 or 1.

Inflammatory eruptions

Skin eruptions of varying morphology have been described in the early weeks after initiation of sorafenib (all grade, 10-60%), sunitinib (all grade, 13-24%), and pazopanib (all grade, 6-8%). Morbilliform eruptions beginning on the face with centripetal spread are most common, but chloracne-like eruption,¹⁵⁴ erythema multiforme-like eruption,¹⁵⁵ toxic epidermal necrolysis, and drug hypersensitivity syndromes have been reported.¹²

Hair changes

Hair changes in texture, density, and color can be seen with multikinase inhibitors. Alopecia occurs in up to 44% of sorafenib patients,^{144,156} but less frequently with sunitinib (5-21%)¹² and pazopanib (8-10%).^{143,157,158} Reversible hair depigmentation is seen during therapy with sunitinib (7-14%)¹⁵⁹⁻¹⁶¹ and pazopanib (27-44%).^{143,158} Cutaneous depigmentation



Fig 8. Genital eruption associated with sorafenib. Note the psoriasiform plaques on the scrotum and groin.

may also be seen with pazopanib.¹² Changes in pigmentation of the hair and skin are felt to be related to c-KIT inhibition¹⁵⁹; however, it may not be a direct effect on the KIT receptor.^{12,162}

Genital involvement

Localized eruptions involving the scrotum or vulva extending onto inguinal skin may occur, including erythematous, psoriasiform, lichenoid, and desquamative forms^{163,164} (Fig 8). Penile involvement may result in phimosis.¹²

Other

Reversible yellow discoloration of the skin can be seen in patients who are undergoing sunitinib treatment,¹⁶⁵ possibly because of cutaneous deposition. Sunitinib may induce facial edema¹⁶⁶ and pyoderma gangrenosum-like ulcerations.¹⁶⁷ Eruptive nevi may occur with sunitinib or sorafenib.¹⁶⁸⁻¹⁷⁰ Sorafenib may induce hyperkeratotic squamoproliferative lesions similar to those seen with BRAF inhibitors.¹⁷¹⁻¹⁷⁸ Asymptomatic subungual splinter hemorrhages are commonly seen in both sorafenib and sunitinib patients.¹⁶⁴ Acute folliculitis, xerosis, photosensitivity, and the development of blue-gray macules of dyspigmentation may occur with vandetanib.¹⁴⁶ As a general rule, these are reversible effects after treatment is discontinued.

CONCLUSION

Cutaneous adverse effects are among the most frequently observed, with many targeted therapies. Dermatologists can provide a useful role in early recognition and mitigation of skin-related toxicities, thereby influencing the need for dose-reduction or drug discontinuation. With continued expansion of the family of targeted therapies, providers caring for those with cutaneous conditions will become integral components to the multidisciplinary team approach of oncologic care.

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REFERENCES

1. Agha R, Kinahan K, Bennett CL, Lacouture ME. Dermatologic challenges in cancer patients and survivors. *Oncology (Williston Park)*. 2007;21:1462-1472, discussion 1473, 1476, 1481 *passim*.
2. Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *CA Cancer J Clin*. 2013;63:249-279.
3. Eilers RE Jr, Gandhi M, Patel JD, et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *J Natl Cancer Inst*. 2010;102: 47-53.
4. Joshi SS, Ortiz S, Witherspoon JN, et al. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. *Cancer*. 2010;116:3916-3923.
5. Balagula Y, Rosen ST, Lacouture ME. The emergence of supportive oncodermatology: the study of dermatologic adverse events to cancer therapies. *J Am Acad Dermatol*. 2011;65:624-635.
6. Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. *J Am Acad Dermatol*. 2008;58:545-570.
7. Osio A, Mateus C, Soria JC, et al. Cutaneous side-effects in patients on long-term treatment with epidermal growth factor receptor inhibitors. *Br J Dermatol*. 2009;161:515-521.
8. Borovicka JH, Calahan C, Gandhi M, et al. Economic burden of dermatologic adverse events induced by molecularly targeted cancer agents. *Arch Dermatol*. 2011;147:1403-1409.
9. Trott A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003;13:176-181.
10. Chen AP, Setser A, Anadkat MJ, et al. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. *J Am Acad Dermatol*. 2012;67:1025-1039.
11. Johnston JB, Navaratnam S, Pitz MW, et al. Targeting the EGFR pathway for cancer therapy. *Curr Med Chem*. 2006;13: 3483-3492.
12. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. *Semin Oncol*. 2012;39:227-240.
13. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer*. 2006;6:803-812.
14. Murillas R, Larcher F, Conti CJ, Santos M, Ullrich A, Jorcano JL. Expression of a dominant negative mutant of epidermal growth factor receptor in the epidermis of transgenic mice elicits striking alterations in hair follicle development and skin structure. *EMBO J*. 1995;14:5216-5223.
15. Brodell LA, Hepper D, Lind A, Gru AA, Anadkat MJ. Histopathology of acneiform eruptions in patients treated with epidermal growth factor receptor inhibitors. *J Cutan Pathol*. 2013;40:865-870.
16. Green MR, Couchman JR. Differences in human skin between the epidermal growth factor receptor distribution detected by EGF binding and monoclonal antibody recognition. *J Invest Dermatol*. 1985;85:239-245.
17. Rodeck U. Skin toxicity caused by EGFR antagonists—an autoinflammatory condition triggered by deregulated IL-1 signaling? *J Cell Physiol*. 2009;218:32-34.
18. Pérez-Soler R. Can rash associated with HER1/EGFR inhibition be used as a marker of treatment outcome? *Oncology (Williston Park)*. 2003;17(11 suppl 12):23-28.

19. Bangsgaard N, Houtkamp M, Schuurhuis DH, et al. Neutralization of IL-8 prevents the induction of dermatologic adverse events associated with the inhibition of epidermal growth factor receptor. *PLoS One.* 2012;7:e39706.
20. Perez-Soler R, Zou Y, Li T, Ling YH. The phosphatase inhibitor menadione (vitamin K3) protects cells from EGFR inhibition by erlotinib and cetuximab. *Clin Cancer Res.* 2011;17:6766-6777.
21. Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. *Curr Oncol.* 2010;17(suppl 1):S18-S30.
22. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med.* 2004;351:337-345.
23. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 2011;19:1079-1095.
24. Segal S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol.* 2005;16:1425-1433.
25. Segal S, Chiribes G, Lemmens L, Dumon K, Van Cutsem E, Tejpar S. Skin toxicities of targeted therapies. *Eur J Cancer.* 2009;45(suppl 1):295-308.
26. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med.* 2005;353:172-187.
27. Roé E, García Muret MP, Marcuelló E, Capdevila J, Pallarés C, Alomar A. Description and management of cutaneous side effects during cetuximab or erlotinib treatments: a prospective study of 30 patients. *J Am Acad Dermatol.* 2006;55:429-437.
28. Luu M, Lai SE, Patel J, Guitart J, Lacouture ME. Photosensitive rash due to the epidermal growth factor receptor inhibitor erlotinib. *Photodermatol Photoimmunol Photomed.* 2007;23:42-45.
29. Jatoi A, Thrower A, Sloan JA, et al. Does sunscreen prevent epidermal growth factor receptor (EGFR) inhibitor-induced rash? Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N05C4). *Oncologist.* 2010;15:1016-1022.
30. Bossi P, Liberatoscioli C, Bergamini C, et al. Previously irradiated areas spared from skin toxicity induced by cetuximab in six patients: implications for the administration of EGFR inhibitors in previously irradiated patients. *Ann Oncol.* 2007;18:601-602.
31. Amador ML, Oppenheimer D, Perea S, et al. An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors. *Cancer Res.* 2004;64:9139-9143.
32. Moreno Garcia V, Thavas P, Blanco Codesido M, et al. Association of creatine kinase and skin toxicity in phase I trials of anticancer agents. *Br J Cancer.* 2012;107:1797-1800.
33. Liu HB, Wu Y, Lv TF, et al. Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One.* 2013;8:e55128.
34. Byun HJ, Lee HJ, Yang JI, et al. Daily skin care habits and the risk of skin eruptions and symptoms in cancer patients. *Ann Oncol.* 2012;23:1992-1998.
35. Fischer A, Rosen AC, Ensslin CJ, Wu S, Lacouture ME. Pruritus to anticancer agents targeting the EGFR, BRAF, and CTLA-4. *Dermatol Ther.* 2013;26:135-148.
36. Jacot W, Bessis D, Jordi E, et al. Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol.* 2004;151:238-241.
37. Lacouture ME, Basti S, Patel J, Benson A 3rd. The SERIES clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. *J Support Oncol.* 2006;4:236-238.
38. Scope A, Agero AL, Dusza SW, et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol.* 2007;25:5390-5396.
39. Jatoi A, Dakhil SR, Sloan JA, et al. Prophylactic tetracycline does not diminish the severity of epidermal growth factor receptor (EGFR) inhibitor-induced rash: results from the North Central Cancer Treatment Group (Supplementary N03CB). *Support Care Cancer.* 2011;19:1601-1607.
40. Jatoi A, Rowland K, Sloan JA, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer.* 2008;113:847-853.
41. Vezzoli P, Marzano AV, Onida F, et al. Cetuximab-induced acneiform eruption and the response to isotretinoin. *Acta Derm Venereol.* 2008;88:84-86.
42. Gutzmer R, Werfel T, Mao R, Kapp A, Elsner J. Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol.* 2005;153:849-851.
43. Bidoli P, Cortinovis DL, Colombo I, et al. Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer. *J Thorac Oncol.* 2010;5:1662-1663.
44. Busam KJ, Capodieci P, Motzer R, Kiehn T, Phelan D, Halpern AC. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol.* 2001;144:1169-1176.
45. Segal S, Tabernero J, Chosidow O, et al. The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. *J Dtsch Dermatol Ges.* 2005;3:599-606.
46. Segal S, Van Cutsem E. Clinical management of EGFR dermatologic toxicities: the European perspective. *Oncology (Williston Park).* 2007;21(11 suppl 5):22-26.
47. Vincenzi B, Tonini G, Santini D. Aprepitant for erlotinib-induced pruritus. *N Engl J Med.* 2010;363:397-398.
48. Gerber PA, Buhren BA, Homey B. More on aprepitant for erlotinib-induced pruritus. *N Engl J Med.* 2011;364:486-487.
49. Zheng S, Pan YL, Wang JL, et al. Gefitinib-induced hair alterations. *BMJ Case Rep.* doi: <http://dx.doi.org/10.1136/bcr.09.2008.0878>. Published online March 17, 2009.
50. Cohen PR, Escudier SM, Kurzrock R. Cetuximab-associated elongation of the eyelashes: case report and review of eyelash trichomegaly secondary to epidermal growth factor receptor inhibitors. *Am J Clin Dermatol.* 2011;12:63-67.
51. Rodriguez NA, Ascaso FJ. Trichomegaly and poliosis of the eyelashes during cetuximab treatment of metastatic colorectal cancer. *J Clin Oncol.* 2011;29:e532-e533.
52. Criado PR, Lima AA. Blepharitis and trichomegaly induced by cetuximab. *An Bras Dermatol.* 2010;85:919-920.
53. Fabbrocini G, Panariello L, Cacciapuoti S, Bianca D, Ayala F. Trichomegaly of the eyelashes during therapy with epidermal growth factor receptor inhibitors: report of 3 cases. *Dermatitis.* 2012;23:237-238.
54. Fraunfelder FT, Fraunfelder FW. Trichomegaly and other external eye side effects associated with epidermal growth factor. *Cutan Ocul Toxicol.* 2012;31:195-197.

55. Morris LG, Hochster HS, Delacure MD. Eyelash trichomegaly secondary to panitumumab therapy. *Curr Oncol.* 2011;18:145-146.
56. Munoz J, Hanbali AS. Epidermal growth factor receptor-induced hirsutism and trichomegaly. *Mayo Clin Proc.* 2011;86:e50.
57. Melichar B, Nemcova I. Eye complications of cetuximab therapy. *Eur J Cancer Care (Engl).* 2007;16:439-443.
58. Pascual JC, Bañuls J, Belinchon I, Blanes M, Massuti B. Trichomegaly following treatment with gefitinib (ZD1839). *Br J Dermatol.* 2004;151:1111-1112.
59. Pongpudpunt M, Demierre MF, Goldberg LJ. A case report of inflammatory nonscarring alopecia associated with the epidermal growth factor receptor inhibitor erlotinib. *J Cutan Pathol.* 2009;36:1303-1307.
60. Yang BH, Bang CY, Byun JW, et al. A case of cicatricial alopecia associated with erlotinib. *Ann Dermatol.* 2011;23(suppl 3):S350-S353.
61. Garden BC, Wu S, Lacouture ME. The risk of nail changes with epidermal growth factor receptor inhibitors: a systematic review of the literature and meta-analysis. *J Am Acad Dermatol.* 2012;67:400-408.
62. Chang GC, Yang TY, Chen KC, Yin MC, Wang RC, Lin YC. Complications of therapy in cancer patients: Case 1. Paronychia and skin hyperpigmentation induced by gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol.* 2004;22:4646-4648.
63. Fox LP. Nail toxicity associated with epidermal growth factor receptor inhibitor therapy. *J Am Acad Dermatol.* 2007;56:460-465.
64. Kerob D, Dupuy A, Reygagne P, et al. Facial hypertrichosis induced by Cetuximab, an anti-EGFR monoclonal antibody. *Arch Dermatol.* 2006;142:1656-1657.
65. Lee MW, Seo CW, Kim SW, et al. Cutaneous side effects in non-small cell lung cancer patients treated with Iressa (ZD1839), an inhibitor of epidermal growth factor. *Acta Derm Venereol.* 2004;84:23-26.
66. Wnorowski AM, de Souza A, Chachoua A, Cohen DE. The management of EGFR inhibitor adverse events: a case series and treatment paradigm. *Int J Dermatol.* 2012;51:223-232.
67. Kwon SH, Choi JW, Hong JS, et al. Gefitinib-induced paronychia: response to autologous platelet-rich plasma. *Arch Dermatol.* 2012;148:1399-1402.
68. El-Abaseri TB, Putta S, Hansen LA. Ultraviolet irradiation induces keratinocyte proliferation and epidermal hyperplasia through the activation of the epidermal growth factor receptor. *Carcinogenesis.* 2006;27:225-231.
69. Peus D, Vasa RA, Meves A, Beyerle A, Pittelkow MR. UVB-induced epidermal growth factor receptor phosphorylation is critical for downstream signaling and keratinocyte survival. *Photochem Photobiol.* 2000;72:135-140.
70. Thaler J, Karthaus M, Mineur L, et al. Skin toxicity and quality of life in patients with metastatic colorectal cancer during first-line panitumumab plus FOLFIRI treatment in a single-arm phase II study. *BMC Cancer.* 2012;12:438.
71. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol.* 2013;31:3182-3190.
72. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. *J Clin Oncol.* 2011;29:2904-2909.
73. Severino G, Chillotti C, De Lisa R, Del Zompo M, Arda R. Adverse reactions during imatinib and lansoprazole treatment in gastrointestinal stromal tumors. *Ann Pharmacother.* 2005;39:162-164.
74. Arora B, Kumar L, Sharma A, Wadhwa J, Kochupillai V. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. *Ann Oncol.* 2004;15:358-359.
75. Valeyrie L, Bastuji-Garin S, Revuz J, et al. Adverse cutaneous reactions to imatinib (ST1571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol.* 2003;48:201-206.
76. Wei G, Rafiyath S, Liu D. First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib. *J Hematol Oncol.* 2010;3:47.
77. Lacouture ME, Maitland ML, Segert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer.* 2010;18:509-522.
78. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol.* 2003;21:1637-1647.
79. Kuwano Y, Asahina A, Watanabe R, Fujimoto M, Ihn H, Tamaki K. Heliotrope-like eruption mimicking dermatomyositis in a patient treated with imatinib mesylate for chronic myeloid leukemia. *Int J Dermatol.* 2006;45:1249-1251.
80. Basso FG, Boer CC, Corrêa ME, et al. Skin and oral lesions associated to imatinib mesylate therapy. *Support Care Cancer.* 2009;17:465-468.
81. Hensley ML, Ford JM. Imatinib treatment: specific issues related to safety, fertility. *pregnancy.* *Semin Hematol.* 2003;40(2 suppl 2):21-25.
82. Besmer P, Manova K, Dutlinger R, et al. The kit-ligand (steel factor) and its receptor c-kit/W: pleiotropic roles in gametogenesis and melanogenesis. *Dev Suppl.* 1993:125-137.
83. Cario-André M, Ardilouze L, Pain C, Gauthier Y, Mahon FX, Taieb A. Imatinib mesilate inhibits melanogenesis in vitro. *Br J Dermatol.* 2006;155:493-494.
84. Huang X, Patel S, Ahmed N, Seiter K, Liu D. Severe toxicity of skin rash, fever and diarrhea associated with imatinib: case report and review of skin toxicities associated with tyrosine kinase inhibitors. *Drug Des Devel Ther.* 2009;2:215-219.
85. Samimi S, Chu E, Seykora J, et al. Dasatinib-induced leukotrichia in a patient with chronic myelogenous leukemia. *JAMA Dermatol.* 2013;149:637-639.
86. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. *Dermatol Ther.* 2011;24:386-395.
87. Legros L, Cassuto JP, Ortonne JP. Imatinib mesilate (Glivec): a systemic depigmenting agent for extensive vitiligo? *Br J Dermatol.* 2005;153:691-692.
88. Kawakami T, Kawanabe T, Soma Y. Cutaneous lichenoid eruption caused by imatinib mesylate in a Japanese patient with chronic myeloid leukaemia. *Acta Derm Venereol.* 2009;89:325-326.
89. Kuraishi N, Nagai Y, Hasegawa M, Ishikawa O. Lichenoid drug eruption with palmoplantar hyperkeratosis due to imatinib mesylate: a case report and a review of the literature. *Acta Derm Venereol.* 2010;90:73-76.
90. Brazzelli V, Muzio F, Manna G, et al. Photoinduced dermatitis and oral lichenoid reaction in a chronic myeloid leukemia patient treated with imatinib mesylate. *Photodermatol Photomed.* 2012;28:2-5.

91. Ena P, Chiarolini F, Siddi GM, Cossu A. Oral lichenoid eruption secondary to imatinib (Glivec). *J Dermatolog Treat.* 2004;15: 253-255.
92. Lim DS, Muir J. Oral lichenoid reaction to imatinib (STI 571, Gleevec). *Dermatology.* 2002;205:169-171.
93. Pascual JC, Matarredona J, Miralles J, Conesa V, Borras-Blasco J. Oral and cutaneous lichenoid reaction secondary to imatinib: report of two cases. *Int J Dermatol.* 2006;45: 1471-1473.
94. Roux C, Boisseau-Garsaud AM, Saint-Cyr I, Hélon R, Quist D, Delaunay C. Lichenoid cutaneous reaction to imatinib [in French]. *Ann Dermatol Venereol.* 2004;131(6-7 pt 1): 571-573.
95. Wahiduzzaman M, Pubalan M. Oral and cutaneous lichenoid reaction with nail changes secondary to imatinib: report of a case and literature review. *Dermatol Online J.* 2008;14:14.
96. Dickens E, Lewis F, Bienz N. Imatinib: a designer drug, another cutaneous complication. *Clin Exp Dermatol.* 2009; 34:603-604.
97. Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol.* 2006;5:228-231.
98. Brazzelli V, Prestinari F, Roveda E, et al. Pityriasis rosea-like eruption during treatment with imatinib mesylate: description of 3 cases. *J Am Acad Dermatol.* 2005;53(5 suppl 1): S240-S243.
99. Konstantopoulos K, Papadogianni A, Dimopoulou M, Kourelis C, Meletis J. Pityriasis rosea associated with imatinib (STI571, Gleevec). *Dermatology.* 2002;205:172-173.
100. Cho AY, Kim DH, Im M, Lee Y, Seo YJ, Lee JH. Pityriasis rosea-like drug eruption induced by imatinib mesylate (Gleevec). *Ann Dermatol.* 2011;23(suppl 3):S360-S363.
101. Brouard MC, Prins C, Mach-Pascual S, Saurat JH. Acute generalized exanthematous pustulosis associated with STI571 in a patient with chronic myeloid leukemia. *Dermatology.* 2001;203:57-59.
102. Gambillara E, Laffitte E, Widmer N, et al. Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukemia. *Dermatology.* 2005; 211:363-365.
103. Schwarz M, Kreuzer KA, Baskaynak G, Dörken B, le Coutre P. Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol.* 2002;69:254-256.
104. Le Nouail P, Viseux V, Chaby G, Billet A, Denoeux JP, Lok C. Drug reaction with eosinophilia and systemic symptoms (DRESS) following imatinib therapy [in French]. *Ann Dermatol Venereol.* 2006;133(8-9 pt 1):686-688.
105. Mahapatra M, Mishra P, Kumar R. Imatinib-induced Stevens-Johnson syndrome: recurrence after re-challenge with a lower dose. *Ann Hematol.* 2007;86:537-538.
106. Ayirookuzhi SJ, Ma L, Ramshesh P, Mills G. Imatinib-induced sweet syndrome in a patient with chronic myeloid leukemia. *Arch Dermatol.* 2005;141:368-370.
107. Kaune KM, Baumgart M, Gesk S, et al. Bullous sweet syndrome in a patient with t(9;22)(q34;q11)-positive chronic myeloid leukemia treated with the tyrosine kinase inhibitor nilotinib: interphase cytogenetic detection of BCR-ABL-positive lesional cells. *Arch Dermatol.* 2008;144: 361-364.
108. Liu D, Seiter K, Mathews T, Madahar CJ, Ahmed T. Sweet's syndrome with CML cell infiltration of the skin in a patient with chronic-phase CML while taking imatinib mesylate. *Leuk Res.* 2004;28(suppl 1):S61-S63.
109. Rousselot P, Larghero J, Raffoux E, et al. Photosensitization in chronic myelogenous leukaemia patients treated with imatinib mesylate. *Br J Haematol.* 2003;120:1091-1092.
110. Clark SH, Duvic M, Prieto VG. Mycosis fungoides-like reaction in a patient treated with Gleevec. *J Cutan Pathol.* 2003;30: 279-281.
111. Breccia M, Latagliata R, Carmosino I, Mandelli F, Alimena G. Reactivation of porphyria cutanea tarda as a possible side effect of Imatinib at high dosage in chronic myeloid leukemia. *Leukemia.* 2004;18:182.
112. Ho AY, Deacon A, Osborne G, Mufti GJ. Precipitation of porphyria cutanea tarda by imatinib mesylate? *Br J Haematol.* 2003;121:375.
113. Drummond A, Micallef-Eynaud P, Douglas WS, Hay I, Holyoake TL, Drummond MW. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI 571, Gleevec). *Br J Haematol.* 2003;120:911-913.
114. de Masson A, Bouvresse S, Clérici T, Mahé E, Saïag P. Recurrent neutrophilic panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib mesilate and dasatinib [in French]. *Ann Dermatol Venereol.* 2011;138: 135-139.
115. Llamas-Velasco M, Steegmann JL, Carrascosa R, Fraga J, García Diez A, Requena L. Perforating folliculitis in a patient treated with nilotinib: a further evidence of C-kit involvement. *Am J Dermopathol.* 2014;36:592-593.
116. Banka N, Aljurf M, Hamadah I. Imatinib (STI-571)-induced exfoliative dermatitis in a Saudi patient with deck chair sign. *Dermatology.* 2003;207:329-330.
117. Mathew T, Chandrashekhar L, Pulimood S, Srivastava A. Imatinib-induced erythroderma. *Australas J Dermatol.* 2007; 48:193-194.
118. Oztas P, Erbasi S, Lenk N, et al. Imatinib-induced erythrodermia in a patient with chronic myeloid leukemia. *Acta Derm Venereol.* 2006;86:174-175.
119. Raj A, Rai R, Rangarajan B. Exfoliative dermatitis with leukemia cutis in a patient with chronic myeloid leukemia: a rare association. *Indian J Dermatol Venereol Leprol.* 2011;77: 208-210.
120. Sanghavi SA, Dongre AM, Khopkar US. Imatinib mesylate induced erythroderma. *Indian J Dermatol Venereol Leprol.* 2012;78:408.
121. Vano-Galvan S, Fernandez-Guarino M, Henriquez-Santana A, De Las Heras E, Calbacho M, Jaen P. Imatinib-induced erythroderma mediated by an unusual non-dose-dependent mechanism. *Eur J Dermatol.* 2007;17:538-539.
122. Hansen T, Little AJ, Miller JJ, Ioffreda MD. A case of inflammatory nonscarring alopecia associated with the tyrosine kinase inhibitor nilotinib. *JAMA Dermatol.* 2013;149: 330-332.
123. Markham T, Mullan R, Golden-Mason L, et al. Resolution of endothelial activation and down-regulation of Tie2 receptor in psoriatic skin after infliximab therapy. *J Am Acad Dermatol.* 2006;54:1003-1012.
124. Roskoski R Jr. Vascular endothelial growth factor (VEGF) signaling in tumor progression. *Crit Rev Oncol Hematol.* 2007; 62:179-213.
125. Cunha SL, Pietras K. ALK1 as an emerging target for antiangiogenic therapy of cancer. *Blood.* 2011;117:6999-7006.
126. Roskoski R Jr. VEGF receptor protein-tyrosine kinases: structure and regulation. *Biochem Biophys Res Commun.* 2008;375:287-291.
127. Wozel G, Sticherling M, Schon MP. Cutaneous side effects of inhibition of VEGF signal transduction. *J Dtsch Dermatol Ges.* 2010;8:243-249.

128. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol.* 2009;6: 465-477.
129. Ganapathi AM, Westmoreland T, Tyler D, Mantyh CR. Bevacizumab-associated fistula formation in postoperative colorectal cancer patients. *J Am Coll Surg.* 2012;214:582-588.
130. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol.* 2005;91: 173-180.
131. Cortés J, Caralt M, Delaloge S, et al. Safety of bevacizumab in metastatic breast cancer patients undergoing surgery. *Eur J Cancer.* 2012;48:475-481.
132. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2006;24:4293-4300.
133. Blumenschein GR Jr, Gatzemeier U, Fossella F, et al. Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. *J Clin Oncol.* 2009;27:4274-4280.
134. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10:25-34.
135. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009;27:3312-3318.
136. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378-390.
137. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006;24:2505-2512.
138. Ryan CW, Goldman BH, Lara PN Jr, et al. Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: a phase II study of the Southwest Oncology Group. *J Clin Oncol.* 2007;25:3296-3301.
139. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet.* 2006;368:1329-1338.
140. Gore ME, Szczylk C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol.* 2009;10:757-763.
141. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356:115-124.
142. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA.* 2006;295: 2516-2524.
143. Hurwitz HI, Dowlati A, Saini S, et al. Phase I trial of pazopanib in patients with advanced cancer. *Clin Cancer Res.* 2009;15: 4220-4227.
144. Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. *Arch Dermatol.* 2008;144:886-892.
145. Lipworth AD, Rober C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology.* 2009;77:257-271.
146. Giacchero D, CRamacciotti, Arnault JP, et al. A new spectrum of skin toxic effects associated with the multikinase inhibitor vandetanib. *Arch Dermatol.* 2012;148:1418-1420.
147. Lacouture ME, Reilly LM, Gerami P, Guitart J. Hand foot skin reaction in cancer patients treated with the multikinase inhibitors sorafenib and sunitinib. *Ann Oncol.* 2008;19: 1955-1961.
148. Yang CH, Lin WC, Chuang CK, et al. Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol.* 2008;158:592-596.
149. Jain L, Gardner ER, Figg WD, Chernick MS, Kong HH. Lack of association between excretion of sorafenib in sweat and hand-foot skin reaction. *Pharmacotherapy.* 2010;30:52-56.
150. Blanchet B, Billemont B, Barete S, et al. Toxicity of sorafenib: clinical and molecular aspects. *Expert Opin Drug Saf.* 2010;9: 275-287.
151. Wolf SL, Qin R, Menon SP, et al. Placebo-controlled trial to determine the effectiveness of a urea/lactic acid-based topical keratolytic agent for prevention of capecitabine-induced hand-foot syndrome: North Central Cancer Treatment Group Study N05C5. *J Clin Oncol.* 2010;28:5182-5187.
152. Kang YK, Lee SS, Yoon DH, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. *J Clin Oncol.* 2010;28:3824-3829.
153. Anderson R, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). *Oncologist.* 2009;14:291-302.
154. Pickert A, Hughes M, Wells M. Chloracne-like drug eruption associated with sorafenib. *J Drugs Dermatol.* 2011;10:1331-1334.
155. MacGregor JL, Silvers DN, Grossman ME, Sherman WH. Sorafenib-induced erythema multiforme. *J Am Acad Dermatol.* 2007;56:527-528.
156. Kong HH, Turner ML. Array of cutaneous adverse effects associated with sorafenib. *J Am Acad Dermatol.* 2009;61: 360-361.
157. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2010;28:475-480.
158. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28:1061-1068.
159. Hartmann JT, Kanz L. Sunitinib and periodic hair depigmentation due to temporary c-KIT inhibition. *Arch Dermatol.* 2008;144:1525-1526.
160. Robert C, Spatz A, Faivre S, Armand JP, Raymond E. Tyrosine kinase inhibition and grey hair. *Lancet.* 2003;361:1056.
161. Lee WJ, Lee JL, Chang SE, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Br J Dermatol.* 2009;161: 1045-1051.
162. Bible KC, Suman VJ, Molina JR, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol.* 2010;11:962-972.
163. Billemont B, Barete S, Rixe O. Scrotal cutaneous side effects of sunitinib. *N Engl J Med.* 2008;359:975-976.
164. Robert C, Mateus C, Spatz A, Wechsler J, Escudier B. Dermatologic symptoms associated with the multikinase inhibitor sorafenib. *J Am Acad Dermatol.* 2009;60:299-305.
165. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol.* 2005; 6:491-500.
166. Guevremont C, Alasker A, Karakiewicz PI. Management of sorafenib, sunitinib, and temsirolimus toxicity in metastatic renal cell carcinoma. *Curr Opin Support Palliat Care.* 2009;3: 170-179.

167. Akanay-Diesel S, Hoff NP, Kürle S, et al. Sunitinib induced pyoderma gangrenosum-like ulcerations. *Eur J Med Res.* 2011; 16:491-494.
168. Bennani-Lahlou M, Mateus C, Escudier B, et al. Eruptive nevi associated with sorafenib treatment [in French]. *Ann Dermatol Venereol.* 2008;135:672-674.
169. Kong HH, Sibaud V, Chanco Turner ML, Fojo T, Hornyak TJ, Chevreau C. Sorafenib-induced eruptive melanocytic lesions. *Arch Dermatol.* 2008;144:820-822.
170. Jiménez-Gallo D, Albarrán-Planellés C, Linares-Barrios M, Martínez-Rodríguez A, Báez-Perea JM. Eruptive melanocytic nevi in a patient undergoing treatment with sunitinib. *JAMA Dermatol.* 2013;149:624-626.
171. Arnault JP, Wechsler J, Escudier B, et al. Keratoacanthomas and squamous cell carcinomas in patients receiving sorafenib. *J Clin Oncol.* 2009;27:e59-e61.
172. Dubauskas Z, Kunishige J, Prieto VG, Jonasch E, Hwu P, Tannir NM. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. *Clin Genitourin Cancer.* 2009;7:20-23.
173. Jantzem H, Dupre-Goetghebeur D, Spindler P, Merrer J. Sorafenib-induced multiple eruptive keratoacanthomas [in French]. *Ann Dermatol Venereol.* 2009;136:894-897.
174. Kong HH, Cowen EW, Azad NS, Dahut W, Gutierrez M, Turner ML. Keratoacanthomas associated with sorafenib therapy. *J Am Acad Dermatol.* 2007;56:171-172.
175. Kwon EJ, Kish LS, Jaworsky C. The histologic spectrum of epithelial neoplasms induced by sorafenib. *J Am Acad Dermatol.* 2009;61:522-527.
176. Lynch MC, Straub R, Adams DR. Eruptive squamous cell carcinomas with keratoacanthoma-like features in a patient treated with sorafenib. *J Drugs Dermatol.* 2011;10:308-310.
177. Marquez CB, Smithberger EE, Bair SM, et al. Multiple keratoacanthomas arising in the setting of sorafenib therapy: novel chemoprophylaxis with bexarotene. *Cancer Control.* 2009;16:66-69.
178. Smith KJ, Haley H, Hamza S, Skelton HG. Eruptive keratoacanthoma-type squamous cell carcinomas in patients taking sorafenib for the treatment of solid tumors. *Dermatol Surg.* 2009;35:1766-1770.

Cutaneous adverse effects of targeted therapies

Part II: Inhibitors of intracellular molecular signaling pathways

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Learning objectives

After completing this learning activity, participants should be able to describe the management strategies of cutaneous adverse effects associated with 11 families of targeted therapies currently in prevalent use.

Disclosures

None declared.

The last decade has spawned an exciting new era of oncotherapy in dermatology, including the development of targeted therapies for metastatic melanoma and basal cell carcinoma. Along with skin cancer, deregulation of the PI3K-AKT-mTOR and RAS-RAF-MEK-ERK intracellular signaling pathways contributes to tumorigenesis of a multitude of other cancers, and inhibitors of these pathways are being actively studied. Similar to other classes of targeted therapies, cutaneous adverse effects are among the most frequent toxicities observed with mitogen-activated protein kinase pathway inhibitors, PI3K-AKT-mTOR inhibitors, hedgehog signaling pathway inhibitors, and immunotherapies. Given the rapid expansion of these families of targeted treatments, dermatologists will be essential in offering dermatologic supportive care measures to cancer patients being treated with these agents. Part II of this continuing medical education article reviews skin-related adverse sequelae, including the frequency of occurrence and the implications associated with on- and off-target cutaneous toxicities of inhibitors of the RAS-RAF-MEK-ERK pathway, PI3K-AKT-mTOR pathway, hedgehog signaling pathway, and immunotherapies. (J Am Acad Dermatol 2015;72:221-36.)

Key words: AKT inhibitor; autoimmune adverse effects; autoimmune dermatopathies; B-RAF; dabrafenib; dermatitis; dual inhibitor; dysgeusia; everolimus; hair loss; hedgehog signaling pathway; immunotherapy; immune-related toxicities; ipilimumab; keratoacanthoma; keratosis pilaris; keratotic squamoproliferative lesion; lambrolizumab; loss of taste; MAP kinase pathway; MEK inhibitors; mTOR inhibitor; nivolumab; panniculitis; PD-1 inhibitor; PI3K-AKT-mTOR pathway; PI3 kinase inhibitor; pruritus; RAF inhibitors; rapamycin; RAS; seborheic dermatitis; selumetinib; squamous cell carcinoma; taste alteration; temsirolimus; trametinib; vemurafenib; vitiligo; verrucal keratosis; vismodegib.

RAS-RAF-MEK-ERK PATHWAY

The RAS-RAF-MEK-ERK (mitogen-activated protein kinase [MAPK]) pathway is one of the most frequently deregulated signaling pathways leading to increased cellular proliferation in a broad spectrum of cancers. Patients who are taking inhibitors of the MAPK pathway frequently present

with cutaneous adverse effects (AEs). The extensive interaction of the MAPK pathway with the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway by sharing common inputs and activation through oncogenic RAS (Fig 1) provides a possible mechanism for compensatory signaling and the development of tumor resistance to targeted

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Abbreviations used:

AE:	adverse effect
CIA:	chemotherapy-induced alopecia
CTLA-4:	cytotoxic T lymphocyte-associated antigen 4
EGFR:	epidermal growth factor receptor
HhSP:	hedgehog signaling pathway
MAH:	melanoma-associated hypopigmentation
MAPK:	mitogen-activated protein kinase
MED:	minimal erythema dose
mTOR:	mammalian target of rapamycin
PD-1:	programmed death 1
PTCH1:	patched homologue 1
SCC:	squamous cell carcinoma
SMO:	smoothened homologue
UVA:	ultraviolet A

monotherapy. One approach used to overcome this challenge is to use a dual pathway–targeted approach. However, although this provides increased potential for clinical benefit, it is often accompanied by a greater degree of toxicity, especially to the skin.¹

RAF INHIBITORS

Key points

- Cutaneous eruptions, keratotic squamo-proliferative lesions, and photosensitivity are among the most debilitating skin-related adverse effects of RAF inhibitors
- Preventative measures and conservative treatments generally control most drug-related adverse effects; surgical treatment may be needed for select aggressive neoplasms
- Close interval follow-up appointments optimize supportive care for RAF inhibitor patients, because skin toxicities are numerous

BRAF, an upstream activator in the MAPK pathway, is mutated in approximately 40% to 60% of cutaneous melanomas.² In addition, BRAF is one of the most frequently mutated protein kinases found in all human cancers.³ Malignancies with the highest association with BRAF mutation, the so-called BRAFomas, include hairy cell leukemia (100%), melanoma (~50%), papillary thyroid (~40%), serous ovarian (~30%), colorectal (<10%), and prostate (<10%).^{4,5} The majority of BRAF mutant melanomas contain a substitution of glutamic acid for valine at codon 600 (BRAF V600E). This mutation constitutively activates BRAF kinase, resulting in hyperproliferation of melanocytes.⁶ Targeted therapies of mutated BRAF, such as vemurafenib and dabrafenib, have emerged as successful treatments for patients with metastatic melanoma, both as monotherapy^{7,8} and in

combination with MEK inhibition.⁹ Cutaneous reactions associated with these agents are common and may be dose-limiting. Treatment considerations are outlined below each AE and summarized in Table I.

Cutaneous eruption

Eruptions may occur in up to 68% of patients taking vemurafenib, with up to 8% experiencing grade 3 symptoms (affecting ≥50% body surface area itching or soreness).^{8,10,11} The eruption has most commonly been described as folliculocentric smooth papules that coalesce into broad morbilliform or toxic, erythema-like plaques involving the torso and extremities, with sparing of the head and neck.¹² Associated acute kidney injury has been described.¹³ Histopathology reveals features of exanthematous drug eruption.¹² The use of vemurafenib after initial treatment with ipilimumab may be associated with a higher likelihood of severe skin toxicity.¹⁴

Treatment of eruptions. Emollients and careful observation are sufficient for grade 1 eruptions. Associated symptoms of grade 2 and 3 eruptions can be controlled with antihistamines and topical steroids (class II-III). Severe cases may require a 5- to 7-day course of systemic steroids and/or treatment interruption. If halting treatment is necessitated because of intolerable symptoms, vemurafenib can be reintroduced with a 25% dose reduction after symptoms abate,¹⁵ typically without worsening of the eruption.^{8,12} Hospital admission with intravenous fluid resuscitation and immediate drug discontinuance is needed for the rare grade 4 eruption.

Epidermal neoplasms (ie, squamous cell carcinoma, keratoacanthoma, verrucal keratoses)

Keratinocyte proliferation is characteristic of BRAF inhibitor–induced adverse skin reactions and presents as a broad spectrum of cutaneous toxicities from verrucal keratoses to invasive squamous cell carcinoma (SCC; Fig 2). The mechanism for formation of SCC in patients treated with RAF inhibitors has been a subject of active research. Biochemical studies¹⁶⁻¹⁹ have shown that RAF blockade in wild-type BRAF cells, particularly in the presence of oncogenic RAS mutations (eg, sun-damaged keratinocytes in a patient with melanoma), can lead to paradoxical MAPK pathway activation through dimerization of RAF isomers (BRAF-CRAF, BRAF-AFAR, and CRAF-CRAF).^{18,20,21} Indeed, studies have shown a high prevalence of RAS mutations in cutaneous SCCs developing in

MOLECULAR SIGNALING PATHWAYS

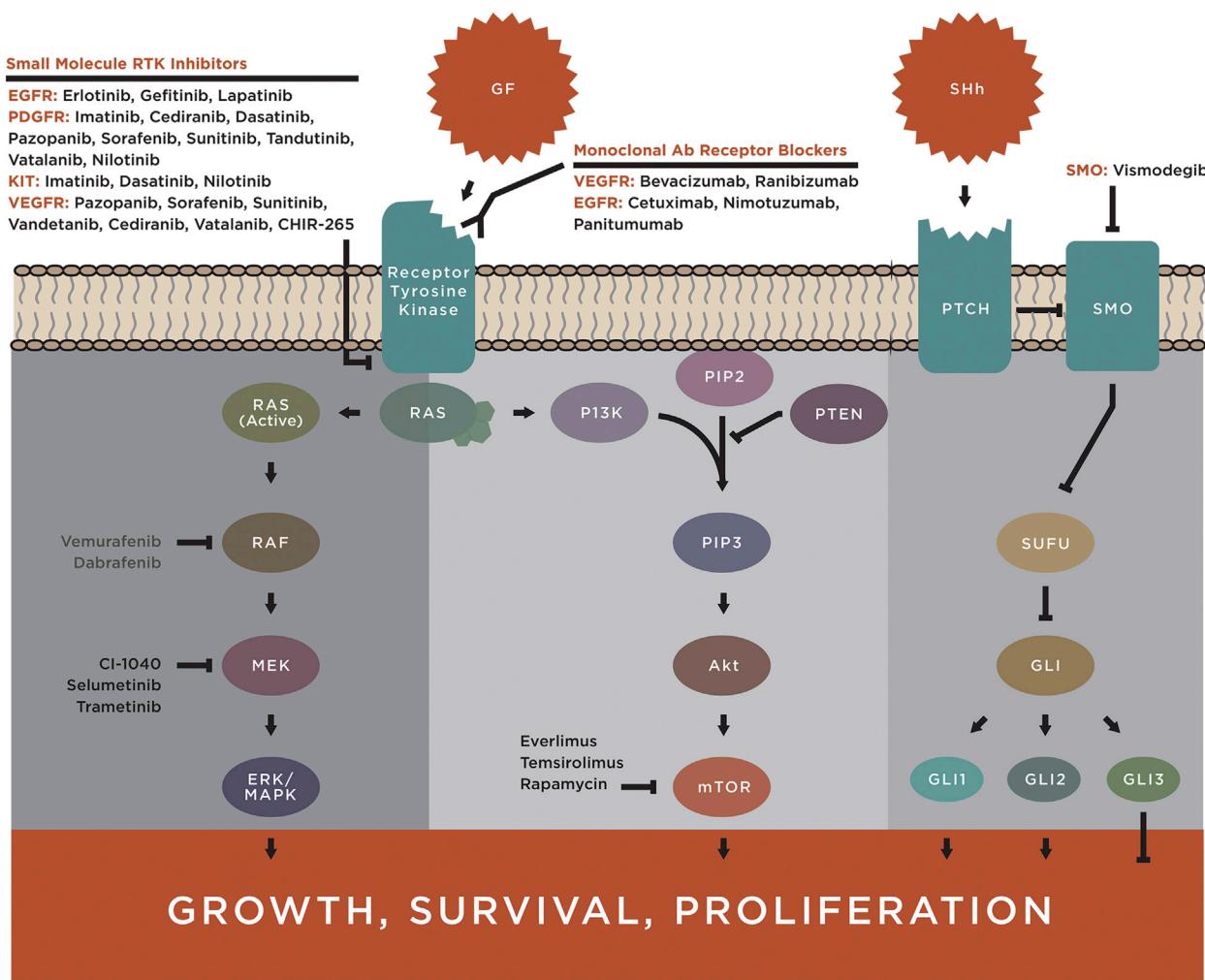


Fig 1. Molecular signaling pathways. Targeted agents listed are meant to be representative and are not intended to be all-inclusive for targeted agent families. *GF*, Growth factor; *RTK*, receptor tyrosine kinase; *SHh*, sonic hedgehog; *SMO*, smoothened.

patients treated with RAF inhibitors, preferentially in lesions arising in sun-damaged skin.^{21,22} Therefore, RAF inhibitor–driven activation of MAPK is thought to not have direct carcinogenic effect but rather unmask the oncogenic events in keratinocytes harboring preexisting sun-induced RAS mutations.²¹ This may account for the rapid appearance of SCCs, sometimes within the first week²³ after initiation of a RAF inhibitor. A similar mechanism has been shown recently in a case of progression of RAS-mutant leukemia during RAF inhibitor treatment.²⁴ Importantly, downstream inhibition of the MAPK pathway by concurrent inhibition of MEK in combination with RAF blockade has been shown to greatly reduce the incidence of squamoproliferative

lesions.⁹ Coinfection with Merkel cell polyomavirus and human papillomavirus-18 within tumoral tissue has been found, leading to the theory that virus-induced transformational processes within keratinocytes may also be involved in SCC oncogenesis.²⁵

Verrucous keratoses,²⁶ characterized by verruciform white keratotic papules occurring in a widespread distribution (in both photoexposed and nonphotoexposed skin; Fig 3), have been described in up to 50% to 86% of studied patients^{23,26,27} and are the most commonly encountered squamoproliferative lesions induced by RAF inhibitors. Pathologically, minimal to mild atypia and lack of viral cytopathologic changes are noted against papillomatosis,

Table I. Management of cutaneous adverse effects of targeted therapies

Targeted therapy class	Agents within class	Dermatologic toxicities	Management	Level of evidence
RAF inhibitors	Vemurafenib and dabrafenib	Rash	Consider temporary treatment stoppage and topical steroids (class I/II) or a short course of systemic steroids	III
		Benign keratotic squamoproliferative lesions (eg, warts and verrucal keratoses)	Destructive treatments: cryotherapy, curettage and electrodesiccation, CO ₂ laser, and PDT; topical treatments: keratolytics, imiquimod, 5-fluorouracil, and ingenol mebutate; excision	III
		Keratoacanthomas and squamous cell carcinoma	If solitary or pauciесional: surgical excision If multiple or eruptive: intralesional 5-fluorouracil, systemic retinoids, and multicycle PDT	III IIA and IIB
		Melanocytic nevi and melanoma	Frequent monitoring with visits every 4-6 weeks Dutiful and strict sun precautions Frequent monitoring with visits every 4-6 weeks at baseline, then every month for first six months of therapy, then every 8 weeks, with dermatoscopy and digital tracking Obtain biopsy specimens of all suspicious lesions Melanoma: wide local excision	III IV IIB
		Keratosis pilaris-like reaction	Gentle skin care; keratolytics and emollients	III
		Seborrheic dermatitis-like eruption	Topical imidazoles and steroids (class VI/VII)	III
		Hyperkeratotic hand-foot skin reaction	Prevention: pretreatment evaluation with podiatrist, orthopedic shoe inserts Management Grade I: emollients and keratolytics Grade II: add topical steroids (class I/II), topical anesthetics, and NSAIDs Grade III: add antiseptic soaks; treatment interruption	IV III
		Photosensitivity	Strict sun avoidance, photoprotective clothing, and broad-spectrum sunscreen daily Topicals: wet dressings, emollients, cooling agents, and steroids (class VI/VII)	IIB
		Panniculitis	Short course of systemic steroids, antihistamines, and NSAIDs	III
		Alopecia	Short course of oral steroids Concealment measures, minoxidil 2-5% continued until 6 months posttherapy	III IIB

MEK inhibitors	CI-1040, selumetinib and trametinib	Morbilliform eruption Papulopustular eruption Xerosis Paronychia	Topical steroids (class III/IV), short course of systemic steroids Preventative measures similar to EGFR inhibitors may be considered (ie, topical steroids, sunscreen and prophylactic tetracyclines) Treatment: low-potency topical steroids (class VI/VII), clindamycin 1% topical, and antiseptic washes Systemic antibiotics: tetracycline class Isotretinoin (20-30 mg/day) Gentle skin care, emollients, antipruritic creams Antiseptic soaks Topical steroids or calcineurin inhibitors Systemic antimicrobials: tetracyclines or culture-driven	III III III III III IB IB III/IB III III
mTOR inhibitors	Rapamycin, everolimus, and temsirolimus	Stomatitis Rash	Topical steroids (class I-III), anesthetics, and antiseptic washes Gentle skin care, wet dressings, emollients, and topical steroids (class III/IV)	III III
Hedgehog pathway inhibitors	Vismodegib	Alopecia Dysgeusia	Concealment measures, minoxidil 2-5% continued until 6 months posttherapy Eliminate extraneous factors of taste alteration (eg, poor oral hygiene, GERD, infection, and postnasal drip) Consider zinc gluconate or sertraline; return of full taste expected after discontinuance	IIB III IIB
Immunomodulators	CTLA-4 inhibitors: ipilimumab and tremelimumab; PD-1 inhibitors: nivolumab and pembrolizumab	Vitiligo Rash Pruritus	Appearance of vitiligo portends favorable response to therapy Gentle skin care, topical steroids (class I-IV), and short courses of systemic steroids; discontinue treatment for grade 3 or 4 eruptions Emollients, antipruritic creams, and antihistamines; consider aprepitant	IIB III IIB

Level of evidence: IA evidence includes evidence from metaanalysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

CTLA-4, Cytotoxic T lymphocyte-associated antigen 4; GERD, gastroesophageal reflux disease; mTOR, mammalian target of rapamycin; NSAID, nonsteroidal antiinflammatory drug; PD-1, programmed death 1; PDT, photodynamic therapy.



Fig 2. Well-differentiated squamous cell carcinoma associated with BRAF inhibitors. Note the crateriform nodule on the left upper back representing well-differentiated squamous cell carcinoma.



Fig 3. Verrucal keratosis associated with BRAF inhibitors. Note the verruciform white papule on the upper eyelid.

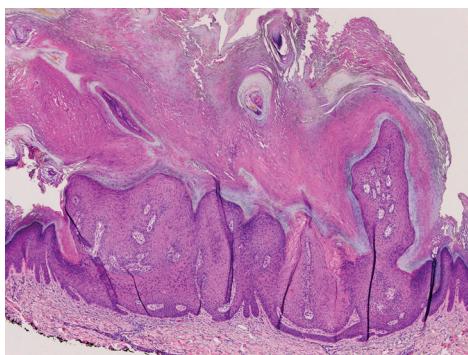


Fig 4. Histopathology of BRAF-associated verrucal keratosis. Note the papillomatosis, acanthosis, hypergranulosis, and hyperkeratosis of the epidermis.

acanthosis, hypergranulosis, and hyperkeratosis^{23,26,28} (Fig 4). Lesions with verrucous architecture have been negative for human papillomavirus immunostaining²³; however, p16 overexpression, a feature of human papillomavirus infection, has been shown.²⁹ While common in both sexes, patients developing verrucal keratoses tend to be older.²⁶ Lesions develop in the first 36 weeks of treatment, with the highest prevalence found



Fig 5. Well-differentiated squamous cell carcinoma associated with BRAF inhibitors.

between 6 and 12 weeks.²⁶ Interestingly, similar-appearing papillomas are known to develop in Costello syndrome, a condition with activating germline HRAS mutations,³⁰ and cardiofaciocutaneous syndrome, in which germline mutations in BRAF, MEK1/2, and KRAS are found,³¹ congruent with the biochemical findings of RAS mutations in squamoproliferative tumors of patients who are taking RAF inhibitors.

Well-differentiated SCCs, including those of keratoacanthoma type (Figs 2 and 5), occur in 20% to 30% of patients.^{8,10,26} Patients who develop SCCs are significantly older than those who do not. The large majority occurs within the first 6 months of treatment, with peak appearance between weeks 12 and 18.²⁶ Pathologically, tumors are well-differentiated, lack acantholysis, often feature keratoacanthoma-like architecture, and generally show mild cytologic atypia.²⁸ Given the similar clinical appearance to the benign verrucal keratoses that can be seen in these patients,^{23,27} a low threshold for obtaining skin biopsy specimens of new lesions is recommended.

Treatment of epidermal neoplasms. Verrucal keratoses have thus far not been shown to be malignant; however, given the variation of epidermal dysplasia²³ and the occasional presence of acantholysis,²⁸ these lesions may potentially represent premalignancies³² and should be monitored closely for changes suggestive of SCC



Fig 6. Keratosis pilaris–like reaction associated with BRAF inhibitors. Note the follicular spiny papules on the lower leg.

(ie, rapid growth, pain, and erythema³²). Early cryotherapy can be very effective.

SCCs have been successfully managed with surgical excision without dose adjustment in most patients taking vemurafenib or dabrafenib.^{7,8,10,11,33} It is not known whether BRAF inhibitor–induced SCC has a different metastatic potential than non–drug-induced cutaneous SCC. Because these lesions can appear in eruptive fashion and most generally regress after treatment is discontinued, a surgical approach may be impractical for all lesions, and noninvasive treatment approaches are needed. If treated early, many lesions can be effectively managed by cryotherapy. 5-Fluorouracil has successfully cleared RAF inhibitor–induced squamoproliferative lesions in a mouse model.³⁴ The intralesional use of 5-fluorouracil with acitretin³⁵ or systemic retinoids alone has been beneficial.³⁶⁻³⁸ Retinoids do not appear to affect RAF inhibitor efficacy.³⁷ Photodynamic therapy has promoted clinical regression in treated lesions after successive cycles.³⁹

In our experience—and in that of others³²—patients with extensive preexisting photodamage may require frequent initial visits, often every 2 to 4 weeks to ensure early identification and management of AEs. The frequency of new lesions often drops after the initial period of treatment.



Fig 7. Seborrheic dermatitis–like eruption associated with BRAF inhibitors. Note the greasy yellow scale with underlying erythema on the scalp.

Keratosis pilaris–like reaction

Diffuse follicular keratotic papules may arise in a generalized distribution clinically resembling keratosis pilaris in roughly 33% of patients^{27,40-42} (Fig 6). Significant pruritus may accompany the eruption.

Keratosis pilaris–like reaction treatment. Topical preparations, including retinoids and those containing urea, alpha-hydroxy acids, or salicylic acid provide comforting relief. Where significant pruritus is involved, topical steroids (class II) and antihistamines are helpful. The eruption generally clears with therapy over the course of several weeks,⁴⁰ while RAF inhibition may continue undisturbed.

Seborrheic dermatitis–like eruption

Pruritic erythematous transient eruptions in a seborrheic distribution may arise during treatment initiation⁴⁰ (Fig 7).

Hyperkeratotic hand–foot reaction

Hyperkeratosis with desquamation developing over sites of friction (Fig 8), namely on the soles, can be debilitating and even dose-limiting. This phenomenon was observed in 6% (5% grade 2; 1% grade 3) of patients in the sentinel vemurafenib study,⁸ but as frequently as 60% of patients in newer studies.^{26,29,40}



Fig 8. Hyperkeratotic hand–foot skin reaction associated with BRAF inhibitors (**A**). Note the desquamation of the fingertip and webspace skin (**B**).

Hyperkeratotic hand–foot reaction

treatment. Avoidance of pressure and friction is the mainstay preventative and therapeutic measure. Spacious footwear and padded gloves decrease frictional strain over pressure points. Other measures include frequent gentle paring of hyperkeratosis and the use of topical steroids (class III–IV) and/or keratolytic medications. Dose reduction or a treatment holiday may be necessary.

Photosensitivity

Grade 2 or 3 photosensitivity eruptions can be seen within the first weeks of treatment with vemurafenib. Dabrafenib has not been as frequently associated with sun sensitivity,⁴³ likely because of its distinct chemical structure. Grade 3 photosensitive eruptions are characterized by blistering and painful erythema that can adversely affect daily activities, including driving. Brief bursts of sun exposure as short as 15 minutes may result in severe burns,¹² with erythema that may develop within minutes of intense exposure.¹² Improvement with broad spectrum sunscreens⁸ and exacerbation while driving a car⁴⁴ prompted the study of minimal erythema dose (MED) tests in vemurafenib patients. Ultraviolet A (UVA) but not ultraviolet B light MED was markedly diminished in all patients and completely reserved after the

application of UVA-tailored sunscreens.⁴⁴ This reaction appears to be niacin- and porphyrin-dependent.⁴⁵

Photosensitivity management. Strict sun precautions are mandatory to prevent painful and even disfiguring burns. Patients are advised regarding sun avoidance, photoprotective clothing, and the dutiful use of broad-spectrum sunscreens. As noted above, UVA protection is of utmost importance.⁴⁴ Potent UVA-blocking agents include titanium dioxide, zinc oxide, ecamazole, and avobenzene. Ultraviolet light–blocking window films can be applied to car, home, and office windows for added protection.

Panniculitis

Selective BRAF inhibitors may induce a painful lobular panniculitis occurring on the upper and lower extremities that may be associated with arthralgias.²⁹ Neutrophilic inflammation predominantly within fat lobules and significant fibrinoid necrosis is typical^{46,47}; however, a chronic infiltrate only may be seen.⁴⁸ Intense pain may result in patients requiring dose adjustments or drug discontinuance.^{12,27,49,50} Most patients have intermittent nodules, and their symptoms improve without interruption of BRAF therapy. Nonsteroidal antiinflammatory drugs provide symptomatic relief.

Melanocytic lesions

BRAF inhibitors may induce dynamic changes in preexisting nevi⁵¹ or eruptive nevi.^{29,42,51} More recently, the development of a second primary melanoma^{52,53}—thus far, BRAF wild-type⁵⁴—has been reported. This is consistent with data indicating that BRAF blockade in wild-type melanoma cells may accelerate cellular proliferation.⁵⁵ In 1 study, up to 21% of patients who were taking vemurafenib had changes in their pigmented lesions that were considered consistent with melanoma.⁵⁶ Although this phenomenon requires more extensive evaluation, available data suggest that patients treated with targeted BRAF inhibitors should undergo regular monitoring of their melanocytic lesions during therapy.

Others

Grade 2 nonscarring alopecia is not infrequently seen in patients starting early in the course of RAF inhibitor treatment,^{8,29} sometimes associated with hair curling.⁴³ Facial erythema,^{29,40} acantholytic dermatoses,⁵⁷ gingival, nipple, and vulvar hyperkeratosis,²⁹ hidradenitis suppurativa (acne inversa),⁴² eruptive milia,¹² epidermoid cysts,²⁹ radiosensitization, and an induction of radiation recall dermatitis,⁵⁸⁻⁶⁰ intense pruritus,^{7,61} hyperkeratosis,⁶² and leiomyoma formation⁶² may be seen. A sarcoidal-type granulomatous eruption in combination BRAF-MEK inhibitor therapy⁶³ has been reported.

MEK INHIBITORS

Key points

- The side effect profile of MEK inhibitors more closely mirrors that of epidermal growth factor receptor inhibitors rather than RAF
- Combination use of MEK and RAF inhibitors improves efficacy and obviates many cutaneous toxicities

Upstream mutations at the level of a tyrosine kinase (ie, epidermal growth factor receptor [EGFR]), RAS, or BRAF can drive constitutive activation within the Raf/MEK/Erk pathway, converging on MEK proteins (MEK1 and MEK2), leading to malignant behavior of cells, increased survival, proliferation, and altered differentiation processes. Recent treatment strategies have focused on the inhibition of MEK in a variety of cancers, including colorectal, pancreatic, non–small cell lung, hepatocellular, and melanoma.⁶⁴⁻⁶⁶ The first selective MEK inhibitor was CI-1040, followed by a second-generation agent (selumetinib) and, later, trametinib. Interestingly, findings thus far in MEK inhibitor studies show



Fig 9. Papulopustular eruption associated with MEK inhibitors. Note the pustule rupture with subsequent crusting and hyperkeratosis in a seborrheic distribution.

cutaneous toxicities that resemble more closely those seen with EGFR inhibitors than those with RAF blockade. Combination therapy of MEK and BRAF inhibitors may mitigate the side effect profile for both drug families. In particular, the paradoxical activation of the MAPK pathway by BRAF inhibitors is abrogated by downstream MEK inhibition, resulting in the development of fewer skin lesions.^{9,55,67,68}

Morbilliform eruption

The most common dose-dependent cutaneous toxicity of MEK inhibitors is an exanthematous morbilliform eruption, occurring in 46% to 74% of patients.⁶⁹⁻⁷¹ Grade 3 or 4 reactions may occur,⁷¹ contributing to dose reduction or temporary discontinuance.⁶⁹

Papulopustular eruption

Another common and potentially dose-limiting AE of MEK inhibitors is an acneiform eruption that primarily involves the head, neck, and upper torso.^{68,71-73} The onset, course, and treatment strategies are very similar to those seen with EGFR inhibitors⁷² (see part I of this continuing medical education article). The eruption may be accompanied by pruritus, sometimes severe, and erythema, weeping, crusting (Fig 9), and superinfection, with the most frequent organism being *Staphylococcus aureus*.⁷²



Fig 10. Paronychia associated with MEK inhibitors.

Xerosis

Dryness, usually accompanied by pruritus, may appear within the first weeks of therapy and tends to follow the same course of onset and progression as the papulopustular eruption.⁷² Xerosis is typically most prominent on the distal extremities, but may be generalized.

Others

Alopecia may affect up to 17% of patients who are taking MEK inhibitors, but is primarily grade 1, and rarely grades 2 or 3.⁷¹ Other toxicities similar to those seen with EGFR inhibitors, including hyperpigmentation, paronychia (Fig 10), trichomegaly, hair depigmentation, and telangiectasia have been described with MEK inhibitors.⁷²⁻⁷⁴

Treatment considerations. Many of the cutaneous toxicities seen in patients who are undergoing MEK inhibitor therapy closely mirror those seen with anti-EGFR therapies (see part I of this continuing medical education article), and the management strategies are similar. Careful monitoring for staphylococcal superinfection of the papulopustular eruption is required, because this occurs with high frequency. Topical or systemic antibiotics according to local antibiograms are necessary. Hand and foot baths with antiseptic additives are useful for paronychia, always in conjunction with emollient use after soaking to prevent xerotic fissures of the fingertips.

PI3K-AKT-mTOR PATHWAY

Aberrant activation of the PI3K-AKT-mTOR pathway occurs in most human malignancies, either from PTEN inactivation or through oncogenic PI3K activity.⁷⁵ Mutated AKT may also independently activate the PI3K-AKT-mTOR signaling pathway in some tumor types.^{76,77} Inhibitors of many targets within this pathway are actively being developed, but we will focus only on the



Fig 11. Morbilliform eruption associated with mammalian target of rapamycin inhibitors.

cutaneous toxicities of mTOR inhibitors in this section. Data for PI3K inhibitors, AKT inhibitors, and dual inhibitors within the pathway are in the early stages of clinical studies and appear to show a similar spectrum of cutaneous toxicities as mTOR inhibitors.

mTOR INHIBITORS

Key points

- **Stomatitis is the most common adverse effect related to therapy with mTOR inhibitors and may necessitate dose adjustment in some cases**
- **Inflammatory eruptions of different types occur with frequency, however these are rarely severe**

The PI3K-AKT-mTOR signaling cascade is an upregulated pathway in multiple malignancies. Beginning with rapamycin, other mTOR inhibitors with enhanced pharmacokinetics and antiproliferative properties, including temsirolimus and everolimus, have now been approved by the US Food and Drug Administration for use in a multitude of cancer types. All the mTOR inhibitors now in use preferentially target mTOR complex-1 and thereby exhibit a similar AE profile. Dermatologic side effects are common and include stomatitis, eruptions, and nail changes, including paronychia.

Stomatitis

Stomatitis related to mTOR inhibitors can be severe and result in dose adjustments or drug cessation.⁷⁸ Stomatitis has been reported in 44% of patients and grade ≥ 3 toxicity in 3%.⁷⁹ In 1 study, dose adjustment or drug discontinuation because of stomatitis occurred in 16% of patients.⁸⁰ mTOR-related mucosal involvement differs from mucositis associated with chemotherapy or radiation by presenting as discrete aphthae on nonkeratinizing

epithelium rather than broad ulceration with pseudomembrane formation.⁷⁹ Its appearance is dose-related and typically seen in isolation, without other sites of gastrointestinal involvement^{78,81}; treatment response is prompt to potent topical steroids.⁸²

Inflammatory eruptions

Inflammatory eruptions have been described with high frequency in treatment with both everolimus (all grade, 25%; grade ≥ 3 , <1%)⁸³ and temsirolimus (all grade, 46%; grade ≥ 3 , 3%).⁷⁹ Several clinical patterns of cutaneous eruptions have been described, including morbilliform (Fig 11), eczematoid, and acneiform.⁸⁴ The onset of the eruption is typically seen during the first couple weeks of treatment.^{78,85} It affects the trunk most frequently, followed by the extremities, neck, face, and scalp.⁸⁶ The primary morphology is erythematous papules and follicle-based pustules.⁸⁶ Mixed histologic patterns of spongiotic, interface, and perivascular are seen.^{79,86} The onset, course, and treatment strategies closely mirror those of the papulopustular eruption seen with EGFR inhibitors (see part I of this continuing medical education article).

Others

Nail toxicity has been reported in 5% to 46% of patients^{80,87-89}; the most common manifestation is paronychia, although pyogenic granuloma-like lesions like those seen with treatment with EGFR inhibitors have also been observed.⁹⁰ Alopecia,⁹¹ facial hypertrichosis,⁹¹ poor wound healing,⁹² pruritus,^{81,93} xerosis,⁹³ edema,⁹⁴ and vasculitis⁹⁵ may also be seen with mTOR inhibitors.

HEDGEHOG SIGNALING PATHWAY INHIBITORS

Key points

- Alopecia is generally reversible and involves <50% of scalp hair; however, widespread hair loss may be seen
- Taste disturbance occurs in $\leq 75\%$ of patients; however, it prompts change in diet habits in a smaller subset of patients

Nearly all basal cell carcinomas have been shown to contain genetic alterations in the hedgehog signaling pathway (HhSP)—the most common being the aberrations leading to loss of function of patched homologue 1 (PTCH1). This allows for constitutive activation of the smoothened homologue (SMO), resulting in unregulated downstream proliferative activity. Vismodegib, a

first-in-class HhSP inhibitor, is a small molecule inhibitor of SMO.

Mucocutaneous toxicities are common in 2 main forms, alopecia (all grade, 58-63%) and dysgeusia (all grade, 51-85%).⁹⁶⁻⁹⁸ Recently, keratoacanthomas⁹⁹ and multiple moderately to well-differentiated SCCs¹⁰⁰ occurring during vismodegib therapy have been described. However, a causal relationship with vismodegib treatment has not yet been established.

Alopecia

Grade 2 hair loss (>50% loss of normal hair that requires that the patient wear a hairpiece and has a great psychosocial impact¹⁰¹) was seen in 10% to 14% of patients.^{96,98} Nonscarring universal alopecia similar to alopecia universalis may also be seen. Although typically reversible, alopecia is perceived by many patients as a significant toxicity of cancer therapies. Among women in 1 study, chemotherapy-induced alopecia (CIA) was considered to be the most troubling side effect of therapy in 58% of patients, and 8% are at risk to avoid therapy altogether because of this potential effect.¹⁰² To date, no pharmacologic therapy can prevent CIA; topical minoxidil has been shown to shorten the duration of hair loss¹⁰³ but not prevent alopecia.^{103,104}

Dysgeusia

The HhSP is known to have activity in the taste papillae^{105,106}; therefore, it is not unexpected that HhSP inhibition may cause taste disturbances.

Grade 1 dysgeusia, defined as altered taste with no change in diet,¹⁰¹ occurred in 29 of 104 (28%) patients in the sentinel vismodegib trial, whereas 24 patients (23%) experienced maximum intensity dysgeusia of grade 2⁹⁶ (altered taste with change of diet [ie, oral supplements], noxious or unpleasant taste, or loss of taste¹⁰¹). Rates of grade 1 dysgeusia have been as high as 57% in subsequent studies.⁹⁹

Dysgeusia management. While full return of taste is observed after targeted treatment is completed, this is an aggravating problem for patients. An assessment for other extraneous factors that contribute to unpleasant taste alteration, including poor oral hygiene, infection, gastroesophageal reflux, and postnasal drip¹⁰⁷ should be performed. No universal treatment for dysgeusia has been established, and several supplements have been shown to have mixed benefit. Zinc gluconate may improve general gustatory function in dysgeusia patients¹⁰⁸; however, another study showed no benefit.¹⁰⁹ The African fruit *Synsepalum*

dulcificum, or “miracle fruit,” has shown modest benefit.¹¹⁰ The free radical scavenger amifostine has been studied in dysgeusia, but while limiting other toxicities, was not helpful with taste alteration.¹¹¹

IMMUNOMODULATORY AGENTS

Key points

- Immune-related adverse effects may include dermatitis, pruritus, and vitiligo
- Symptoms are dose-related, rarely severe, and reversible

Improved understanding of regulatory processes that limit the immune response to cancer has led to emergence of potent immunomodulatory anticancer therapies. This is well illustrated with the development of therapeutic antibodies targeting inhibitory receptors expressed by T cells, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1). These “immune checkpoint” targeted agents show the potential to unleash the immune system against cancer cells and have been shown to induce dramatic and prolonged clinical responses. However, concomitant nonspecific activation of the immune system can also occur, leading to a spectrum of side effects.

CTLA-4 INHIBITORS

Ipilimumab is a recombinant, human monoclonal antibody that binds to CTLA-4. The US Food and Drug Administration approved ipilimumab in 2011 based on increased overall survival in comparison to standard chemotherapy.¹¹² In addition to its antitumor activity, ipilimumab’s immune activating mechanism also causes a heightened immune response against native cellular functions, resulting in a spectrum of autoimmune AEs. Autoimmune dermopathies are the most frequently observed (in 40% of patients), followed by immune-related colitis/diarrhea.¹¹³ Immune-related skin toxicities include pruritus ($\leq 30\%$ of patients¹¹⁴), morbilliform eruption (10-50% of patients¹¹⁴), and vitiligo-like melanoma-associated hypopigmentation (MAH), which portends prognostic favorability.¹¹⁵⁻¹¹⁷ Symptoms appear within 3 to 6 weeks after initiation.¹¹² Less common reactions include prurigo nodularis, lichenoid exanthems, papulopustular eruptions, ulcerations mimicking pyoderma gangrenosum, photosensitivity, and radiation recall.¹¹⁸ Grade 3 or 4 reactions are rare, but may include toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms.¹¹⁸ Symptoms are generally dose-dependent and reverse after treatment is complete.

PD-1 INHIBITORS

The PD-1 inhibitors nivolumab (BMS-936558) and pembrolizumab (formerly lambrolizumab; MK-3475) provided progression-free survival in $\leq 41\%$ and objective responses in $\leq 28\%$ of patients in recent studies^{119,120} and sustained tumor regression in those with disease progression while taking ipilimumab.^{120,121} Additional trials are underway for melanoma, renal cell carcinoma, and non–small cell lung carcinoma. Autoimmune AEs similar to ipilimumab have been seen thus far in clinical trials.^{119,122,123} Skin-related sequelae include vitiligo, various cutaneous eruptions, and pruritus.

CONCLUSION

Cutaneous AEs are among the most frequently observed with many targeted therapies. Dermatologists can provide a useful role in minimizing the impact of skin-related toxicities, thereby influencing the need for dose-reduction or drug stoppage. With continued development of more targeted therapies, providers caring for those with cutaneous conditions will become integral components to the multidisciplinary approach of oncologic care.

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REFERENCES

1. Shimizu T, Tolcher AW, Papadopoulos KP, et al. The clinical effect of the dual-targeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in patients with advanced cancer. *Clin Cancer Res.* 2012;18:2316-2325.
2. Curtin JA, Fridley J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005;353: 2135-2147.
3. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. *Nature.* 2007;446: 153-158.
4. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature.* 2002;417:949-954.
5. Tacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med.* 2011;364:2305-2315.
6. Dhomen N, Marais R. BRAF signaling and targeted therapies in melanoma. *Hematol Oncol Clin North Am.* 2009; 23:529-545.
7. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2012;380:358-365.
8. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364:2507-2516.
9. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med.* 2012;367:1694-1703.
10. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N Engl J Med.* 2010; 363:809-819.

11. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* 2012;366:707-714.
12. Sinha R, Edmonds K, Newton-Bishop JA, Gore ME, Larkin J, Fearfield L. Cutaneous adverse events associated with vemurafenib in patients with metastatic melanoma: practical advice on diagnosis, prevention and management of the main treatment-related skin toxicities. *Br J Dermatol.* 2012; 167:987-994.
13. Regnier-Rosenthal E, Lazareth H, Gressier L, Avril MF, Thervet E, Dupin N. Acute kidney injury in patients with severe rash on vemurafenib treatment for metastatic melanomas. *Br J Dermatol.* 2013;169:934-938.
14. Harding JJ, Pulitzer M, Chapman PB. Vemurafenib sensitivity skin reaction after ipilimumab. *N Engl J Med.* 2012;366:866-868.
15. Datapharm web site. Roche, Zelboraf 240 mg film-coated tablets. Summary of product characteristics. Available at: <http://www.medicines.org.uk/EMC/medicine/26056/SPC/Zelboraf+240+mg+Film-coated+Tablets/>. Accessed August 24, 2014.
16. Hatzivassiliou G, Song K, Yen I, et al. RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. *Nature.* 2010;464:431-435.
17. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell.* 2010;140:209-221.
18. Poulikakos PI, Persaud Y, Janakiraman M, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature.* 2011;480:387-390.
19. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature.* 2010;464:427-430.
20. Sanchez-Laorden B, Viros A, Girotti MR, et al. BRAF inhibitors induce metastasis in RAS mutant or inhibitor-resistant melanoma cells by reactivating MEK and ERK signaling. *Sci Signal.* 2014;7:ra30.
21. Su F, Viros A, Milagre C, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N Engl J Med.* 2012;366:207-215.
22. Oberholzer PA, Kee D, Dziunycz P, et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. *J Clin Oncol.* 2012;30:316-321.
23. Chu EY, Wanat KA, Miller CJ, et al. Diverse cutaneous side effects associated with BRAF inhibitor therapy: a clinicopathologic study. *J Am Acad Dermatol.* 2012;67: 1265-1272.
24. Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. *N Engl J Med.* 2012;367:2316-2321.
25. Falchook GS, Rady P, Hymes S, et al. Merkel cell polyomavirus and HPV-18 associated with cutaneous squamous cell carcinoma arising in a patient with melanoma treated with the BRAF inhibitor dabrafenib. *JAMA Dermatol.* 2013;149: 322-326.
26. Anforth RM, Blumetti TC, Kefford RF, et al. Cutaneous manifestations of dabrafenib (GSK2118436): a selective inhibitor of mutant BRAF in patients with metastatic melanoma. *Br J Dermatol.* 2012;167:1153-1160.
27. Lacouture ME, O'Reilly K, Rosen N, Solit DB. Induction of cutaneous squamous cell carcinomas by RAF inhibitors: cause for concern? *J Clin Oncol.* 2012;30:329-330.
28. Harvey NT, Millward M, Wood BA. Squamoproliferative lesions arising in the setting of BRAF inhibition. *Am J Dermatopathol.* 2012;34:822-826.
29. Boussemaert L, Routier E, Mateus C, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. *Ann Oncol.* 2013;24: 1691-1697.
30. Siegel DH, Mann JA, Krol AL, Rauen KA. Dermatological phenotype in Costello syndrome: consequences of Ras dysregulation in development. *Br J Dermatol.* 2012;166: 601-607.
31. Siegel DH, McKenzie J, Frieden IJ, Rauen KA. Dermatological findings in 61 mutation-positive individuals with cardiofaciocutaneous syndrome. *Br J Dermatol.* 2011;164: 521-529.
32. Anforth R, Fernandez-Péñas P, Long GV. Cutaneous toxicities of RAF inhibitors. *Lancet Oncol.* 2013;14:e11-e18.
33. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet.* 2012;379:1893-1901.
34. Viros A, Hayward R, Martin M, et al. Topical 5-fluorouracil elicits regressions of BRAF inhibitor-induced cutaneous squamous cell carcinoma. *J Invest Dermatol.* 2013;133: 274-276.
35. LaPresto L, Cranmer L, Morrison L, Erickson CP, Curiel-Lewandrowski C. A novel therapeutic combination approach for treating multiple vemurafenib-induced keratoacanthomas: systemic acitretin and intralesional fluorouracil. *JAMA Dermatol.* 2013;149:279-281.
36. Anforth R, Blumetti TC, Mohd Affandi A, Fernandez-Péñas P. Systemic retinoid therapy for chemoprevention of nonmelanoma skin cancer in a patient treated with vemurafenib. *J Clin Oncol.* 2012;30:e165-e167.
37. Sachse MM, Wagner G. Clearance of BRAF inhibitor-associated keratoacanthomas by systemic retinoids. *Br J Dermatol.* 2014;170:475-477.
38. Anforth R, Blumetti TC, Clements A, Kefford R, Long GV, Fernandez-Péñas P. Systemic retinoids for the chemoprevention of cutaneous squamous cell carcinoma and verrucous keratosis in a cohort of patients on BRAF inhibitors. *Br J Dermatol.* 2013;169:1310-1313.
39. Alloo A, Garibyan L, LeBoeuf N, et al. Photodynamic therapy for multiple eruptive keratoacanthomas associated with vemurafenib treatment for metastatic melanoma. *Arch Dermatol.* 2012;148:363-366.
40. Huang V, Hepper D, Anadkat M, Cornelius L. Cutaneous toxic effects associated with vemurafenib and inhibition of the BRAF pathway. *Arch Dermatol.* 2012;148:628-633.
41. Wang CM, Fleming KF, Hsu S. A case of vemurafenib-induced keratosis pilaris-like eruption. *Dermatol Online J.* 2012;18:7.
42. Ma L, Dominguez AR, Collins GR, Kia KF, Cockerell CJ. Hidradenitis suppurativa, eruptive melanocytic nevi, and keratosis pilaris-like eruption in a patient treated with vemurafenib. *Arch Dermatol.* 2012;148:1428-1429.
43. Mandala M, Massi D, De Giorgi V. Cutaneous toxicities of BRAF inhibitors: clinical and pathological challenges and call to action. *Crit Rev Oncol Hematol.* 2013;88:318-337.
44. Dummer R, Rinderknecht J, Goldinger SM. Ultraviolet A and photosensitivity during vemurafenib therapy. *N Engl J Med.* 2012;366:480-481.
45. Gelot P, Dutarte H, Khammari A, et al. Vemurafenib: an unusual UVA-induced photosensitivity. *Exp Dermatol.* 2013; 22:297-298.
46. Kim GH, Levy A, Compagni G. Neutrophilic panniculitis developing after treatment of metastatic melanoma with vemurafenib. *J Cutan Pathol.* 2013;40:667-669.

47. Maldonado-Seral C, Berros-Fombella JP, Vivanco-Allende B, Coto-Segura P, Vazquez-Lopez F, Perez-Oliva N. Vemurafenib-associated neutrophilic panniculitis: an emergent adverse effect of variable severity. *Dermatol Online J.* 2013;19:16.
48. Sinha R, Edmonds K, Newton-Bishop J, Gore M, Larkin J, Fearfield L. Erythema nodosum-like panniculitis in patients with melanoma treated with vemurafenib. *J Clin Oncol.* 2013; 31:e320-e321.
49. Monfort JB, Pagès C, Schneider P, et al. Vemurafenib-induced neutrophilic panniculitis. *Melanoma Res.* 2012;22: 399-401.
50. Zimmer L, Livingstone E, Hillen U, Dömkens S, Becker A, Schadendorf D. Panniculitis with arthralgia in patients with melanoma treated with selective BRAF inhibitors and its management. *Arch Dermatol.* 2012;148:357-361.
51. Haenssle HA, Kraus SL, Brehmer F, et al. Dynamic changes in nevi of a patient with melanoma treated with vemurafenib: importance of sequential dermoscopy. *Arch Dermatol.* 2012; 148:1183-1185.
52. Debarbieux S, Dalle S, Depaepe L, Poualhon N, Balme B, Thomas L. Second primary melanomas treated with BRAF blockers: study by reflectance confocal microscopy. *Br J Dermatol.* 2013;168:1230-1235.
53. Dalle S, Poualhon N, Debarbieux S, Thomas L. Second primary melanomas on treatment with vemurafenib. *Br J Dermatol.* 2013;168:887-888.
54. Zimmer L, Hillen U, Livingstone E, et al. Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. *J Clin Oncol.* 2012;30:2375-2383.
55. King AJ, Arnone MR, Bleam MR, Moss KG, Yang J, Fedorowicz KE, et al. Dabrafenib; preclinical characterization, increased efficacy when combined with trametinib, while BRAF/MEK tool combination reduced skin lesions. *PLoS One.* 2013;8:e67583.
56. Perier-Muzet M, Thomas L, Poualhon N, et al. Melanoma patients under vemurafenib: prospective follow-up of melanocytic lesions by digital dermoscopy. *J Invest Dermatol.* 2014;134:1351-1358.
57. Gupta M, Huang V, Linette G, Cornelius L. Unusual complication of vemurafenib treatment of metastatic melanoma: exacerbation of acantholytic dyskeratosis complicated by Kaposi varicelliform eruption. *Arch Dermatol.* 2012;148:966-968.
58. Boussemart L, Boivin C, Claveau J, et al. Vemurafenib and radiosensitization. *JAMA Dermatol.* 2013;149:855-857.
59. Peuvrel L, Ruellan AL, Thillays F, et al. Severe radiotherapy-induced extracutaneous toxicity under vemurafenib. *Eur J Dermatol.* 2013;23:879-881.
60. Satzger I, Degen A, Asper H, Kapp A, Hauschild A, Gutzmer R. Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy. *J Clin Oncol.* 2013;31:e220-e222.
61. Fischer A, Rosen AC, Ensslin CJ, Wu S, Lacouture ME. Pruritus to anticancer agents targeting the EGFR, BRAF, and CTLA-4. *Dermatol Ther.* 2013;26:135-148.
62. Clarke M, Ortel B, Brockstein B, et al. Bilateral areolar leiomyomas in a patient undergoing BRAF inhibition therapy for melanoma. *J Cutan Pathol.* 2013;40:884-886.
63. Green JS, Norris DA, Wisell J. Novel cutaneous effects of combination chemotherapy with BRAF and MEK inhibitors: a report of two cases. *Br J Dermatol.* 2013;169:172-176.
64. Davies BR, Logie A, McKay JS, et al. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. *Mol Cancer Ther.* 2007;6:2209-2219.
65. Haass NK, Sproesser K, Nguyen TK, et al. The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. *Clin Cancer Res.* 2008;14:230-239.
66. Huynh H, Soo KC, Chow PK, Tran E. Targeted inhibition of the extracellular signal-regulated kinase kinase pathway with AZD6244 (ARRY-142886) in the treatment of hepatocellular carcinoma. *Mol Cancer Ther.* 2007;6:138-146.
67. Gadiot J, Hooijkaas AI, Deken MA, Blank CU. Synchronous BRAF(V600E) and MEK inhibition leads to superior control of murine melanoma by limiting MEK inhibitor induced skin toxicity. *Oncotargets Ther.* 2013;6:1649-1658.
68. Anforth R, Liu M, Nguyen B, et al. Acneiform eruptions: a common cutaneous toxicity of the MEK inhibitor trametinib. *Australas J Dermatol.* 2014;55:250-254.
69. Adjei AA, Cohen RB, Franklin W, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. *J Clin Oncol.* 2008;26:2139-2146.
70. Banerji U, Camidge DR, Verheul HM, et al. The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. *Clin Cancer Res.* 2010;16:1613-1623.
71. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2012;367:107-114.
72. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB, Myskowski PL. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). *Invest New Drugs.* 2011;29: 1114-1121.
73. Desar IM, Bovenschen HJ, Timmer-Bonte AJ, et al. Case studies showing clinical signs and management of cutaneous toxicity of the MEK1/2 inhibitor AZD6244 (ARRY-142886) in patients with solid tumours. *Acta Oncol.* 2010;49:110-113.
74. Schad K, Baumann Conzett K, Zipser MC, et al. Mitogen-activated protein/extracellular signal-regulated kinase kinase inhibition results in biphasic alteration of epidermal homeostasis with keratinocytic apoptosis and pigmentation disorders. *Clin Cancer Res.* 2010;16:1058-1064.
75. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nat Rev Cancer.* 2002;2: 489-501.
76. Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature.* 2007;448:439-444.
77. Davies MA, Stemke-Hale K, Tellez C, et al. A novel AKT3 mutation in melanoma tumours and cell lines. *Br J Cancer.* 2008;99:1265-1268.
78. Soefje SA, Karnad A, Brenner AJ. Common toxicities of mammalian target of rapamycin inhibitors. *Target Oncol.* 2011;6:125-129.
79. Gomez-Fernandez C, Garden BC, Wu S, Feldman DR, Lacouture ME. The risk of skin rash and stomatitis with the mammalian target of rapamycin inhibitor temsirolimus: a systematic review of the literature and meta-analysis. *Eur J Cancer.* 2012;48:340-346.
80. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol.* 2004; 22:909-918.

81. Campistol JM, de Fijter JW, Flechner SM, Langone A, Morelon E, Stockfleth E. mTOR inhibitor-associated dermatologic and mucosal problems. *Clin Transplant.* 2010;24:149-156.
82. Chuang P, Langone AJ. Clobetasol ameliorates aphthous ulceration in renal transplant patients on sirolimus. *Am J Transplant.* 2007;7:714-717.
83. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372:449-456.
84. Sankhala K, Mita A, Kelly K, Mahalingam D, Giles F, Mita M. The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. *Target Oncol.* 2009;4:135-142.
85. Gandhi M, Kuzel T, Lacouture M. Eosinophilic rash secondary to temsirolimus. *Clin Genitourin Cancer.* 2009;7:E34-E36.
86. Balagura Y, Rosen A, Tan BH, et al. Clinical and histopathologic characteristics of rash in cancer patients treated with mammalian target of rapamycin inhibitors. *Cancer.* 2012;118:5078-5083.
87. O'Donnell A, Faivre S, Burris HA 3rd, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. *J Clin Oncol.* 2008;26:1588-1595.
88. Raymond E, Alexandre J, Faivre S, et al. Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. *J Clin Oncol.* 2004;22:2336-2347.
89. Tabernero J, Rojo F, Calvo E, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. *J Clin Oncol.* 2008;26:1603-1610.
90. Raju DL, Bitzan M. Sirolimus-associated chronic pyogenic perungual infection. *Kidney Int.* 2007;71:476.
91. Mahé E, Morelon E, Lechaton S, et al. Cutaneous adverse events in renal transplant recipients receiving sirolimus-based therapy. *Transplantation.* 2005;79:476-482.
92. De Masson A, Fouchard N, Méry-Bossard L, Dauendorffer JN. Cutaneous and mucosal aphthosis during temsirolimus therapy for advanced renal cell carcinoma: review of cutaneous and mucosal side effects of mTOR inhibitors. *Dermatology.* 2011;223:4-8.
93. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. *Semin Oncol.* 2012;39:227-240.
94. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356:2271-2281.
95. Hardinger KL, Cornelius LA, Trulock EP 3rd, Brennan DC. Sirolimus-induced leukocytoclastic vasculitis. *Transplantation.* 2002;74:739-743.
96. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med.* 2012;366:2171-2179.
97. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med.* 2012;366:2180-2188.
98. Chang AL, Solomon JA, Hainsworth JD, et al. Expanded access study of patients with advanced basal cell carcinoma treated with the Hedgehog pathway inhibitor, vismodegib. *J Am Acad Dermatol.* 2014;70:60-69.
99. Aasi S, Silkiss R, Tang JY, et al. New onset of keratoacanthomas after vismodegib treatment for locally advanced basal cell carcinomas: a report of 2 cases. *JAMA Dermatol.* 2013;149:242-243.
100. Orouji A, Goerdt S, Utikal J, Leverkus M. Multiple highly and moderately differentiated squamous cell carcinomas of the skin during Vismodegib treatment of inoperable basal cell carcinoma. *Br J Dermatol.* 2014;171:431-433.
101. Trott A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol.* 2003;13:176-181.
102. McGarvey EL, Baum LD, Pinkerton RC, Rogers LM. Psychological sequelae and alopecia among women with cancer. *Cancer Pract.* 2001;9:283-289.
103. Duvic M, Lemak NA, Valero V, et al. A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol.* 1996;35:74-78.
104. Rodriguez R, Machiavelli M, Leone B, et al. Minoxidil (Mx) as a prophylaxis of doxorubicin-induced alopecia. *Ann Oncol.* 1994;5:769-770.
105. Iwatsuki K, Liu HX, Grónder A, et al. Wnt signaling interacts with Shh to regulate taste papilla development. *Proc Natl Acad Sci U S A.* 2007;104:2253-2258.
106. Liu HX, Macallum DK, Edwards C, Gaffield W, Mistretta CM. Sonic hedgehog exerts distinct, stage-specific effects on tongue and taste papilla development. *Dev Biol.* 2004;276:280-300.
107. Hong JH, Omur-Ozbek P, Stanek BT, et al. Taste and odor abnormalities in cancer patients. *J Support Oncol.* 2009;7:58-65.
108. Halyard MY. Taste and smell alterations in cancer patients—real problems with few solutions. *J Support Oncol.* 2009;7:68-69.
109. Halyard MY, Jatoi A, Sloan JA, et al. Does zinc sulfate prevent therapy-induced taste alterations in head and neck cancer patients? Results of phase III double-blind, placebo-controlled trial from the North Central Cancer Treatment Group (N01C4). *Int J Radiat Oncol Biol Phys.* 2007;67:1318-1322.
110. Wilken MK, Satiroff BA. Pilot study of "miracle fruit" to improve food palatability for patients receiving chemotherapy. *Clin J Oncol Nurs.* 2012;16:E173-E177.
111. Büntzel J, Schuth J, Küttner K, Glatzel M. Radiochemotherapy with amifostine cytoprotection for head and neck cancer. *Support Care Cancer.* 1998;6:155-160.
112. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711-723.
113. Zimmer L, Vaubel J, Livingstone E, Schadendorf D. Side effects of systemic oncological therapies in dermatology. *J Dtsch Dermatol Ges.* 2012;10:475-486.
114. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364:2517-2526.
115. Gogas H, Ioannovich J, Dafni U, et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med.* 2006;354:709-718.
116. Krauze MT, Tarhini A, Gogas H, Kirkwood JM. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *Semin Immunopathol.* 2011;33:385-391.
117. Nordlund JJ, Kirkwood JM, Forget BM, Milton G, Albert DM, Lerner AB. Vitiligo in patients with metastatic melanoma: a good prognostic sign. *J Am Acad Dermatol.* 1983;9:689-696.
118. Voskens CJ, Goldinger SM, Loquai C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One.* 2013;8:e53745.
119. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366:2443-2454.

120. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med.* 2013;369:134-144.
121. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naïve melanoma. *J Clin Oncol.* 2013;31:4311-4318.
122. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366:2455-2465.
123. Lipson EJ, Sharfman WH, Drake CG, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. *Clin Cancer Res.* 2013;19:462-468.

Surgical technique for optimal outcomes

Part I. Cutting tissue: Incising, excising, and undermining

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Learning objectives

After completing this learning activity, participants should be able to describe common errors during the removal of tissue that lead to unaesthetic scars and delineate the steps for proficient fusiform excisions.

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Sound surgical technique is necessary to achieve excellent surgical outcomes. Despite the fact that dermatologists perform more office-based cutaneous surgery than any other specialty, few dermatologists have opportunities for practical instruction to improve surgical technique after residency and fellowship. This 2-part continuing medical education article will address key principles of surgical technique at each step of cutaneous reconstruction. Part I reviews incising, excising, and undermining. Objective quality control questions are proposed to provide a framework for self-assessment and continuous quality improvement. (*J Am Acad Dermatol* 2015;72:377-87.)

Key words: excise; excision; incise; skin; surgery; suture; technique; undermine.

INTRODUCTION

Surgeons influence the aesthetics of scars from cutaneous surgery in 2 ways: (1) surgical design and (2) surgical technique. The principles of aesthetic surgical design are universally accepted, and include preserving and restoring free margins (eg, eyelids, nasal tip and ala, lips, and helical rim), preserving and restoring contour, and placing scars in cosmetic subunit junction lines.¹ Placing scars along relaxed skin tension lines is also desirable, but is less important compared to the aforementioned principles.² For example, it is undesirable to conform to the horizontal relaxed skin tension lines on the forehead if elevation of the ipsilateral eyebrow creates asymmetry.

While surgeons nearly universally adhere to the core principles of aesthetic surgical design, surgical technique varies markedly. These variations can confuse surgical trainees, who are left to struggle by trial and error through numerous potential approaches to execute the same surgical technique.^{3,4} Only after months to years of independent practice and observation of their own postoperative outcomes do most surgeons refine their own surgical technique and achieve reproducibly excellent results.⁵ Many practitioners desire additional surgical coaching after their formal training.⁶ This 2-part continuing medical education article proposes quality control questions for each step of cutaneous reconstruction and provides a

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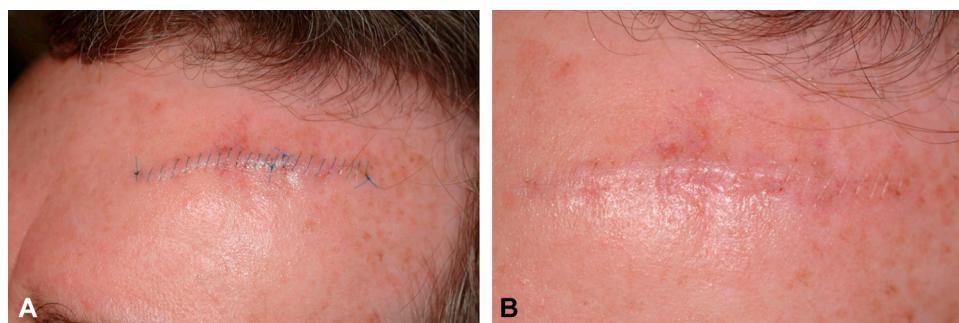


Fig 1. **A**, Ideal appearance of a wound on the forehead 1 week postsurgery, with sutures still in place. There is minimal erythema. **B**, Appearance of the same wound on the forehead immediately after removing the sutures. Precise approximation of the wound edges and minimal inflammation reflect sound surgical technique and portend a minimally apparent scar.

framework for self-assessment and continuous quality improvement.

STEPS OF SURGICAL RECONSTRUCTION

Surgical techniques fall into 2 broad categories: cutting and suturing. Cutting techniques include incising, excising, and undermining. Suturing techniques include placing deep and top sutures. Most reconstructive surgery involves the stepwise execution of these cutting and suturing techniques. Each step influences the success of subsequent steps; errors early in the process make the precise execution of subsequent steps either more difficult or impossible.

Scars heal with a shiny texture that reflects light more brightly than the textured, normal surrounding skin. Sound surgical technique must therefore aim to diminish the contrast between scar and normal skin by minimizing the breadth of the scar.⁷⁻⁹ Precise, tension-free approximation of the skin edges allows for prompt reepithelialization and a barely visible scar.^{10,11} The appearance of scars often improves with time, helping to disguise minor technical deficiencies.¹² The appearance of the wound 1 week after surgery gives an honest assessment of the precision of the surgical technique. Completely reepithelialized scars with minimal to no inflammation signify meticulous surgical technique (Fig 1). Wounds with prominent inflammation and focal inversion or separation of wound edges usually result from suboptimal surgical technique (Fig 2). In these continuing medical education articles, we analyze each step of cutting and suturing and propose quality control checkpoints for objective self-evaluation. Part I reviews cutting techniques, including incising, excising, and undermining. Part II reviews suturing techniques, including placing deep and top sutures. Space precludes a comprehensive coverage of surgical

techniques; we therefore focus on core techniques that apply broadly to any surgeon performing surgery of the skin.

CUTTING TECHNIQUE: INCISING

Key points

- The incision aims to achieve uniform release of the entire skin edge to the desired anatomic depth
- The ideal depth of the incision varies according to the anatomic location and intent of the procedure
- The incised wound edges should be smooth and sharply perpendicular to the skin surface
- Beveling of the dermis or fat toward the center of the wound impedes the precise approximation of wound edges

The goal of the incision is to achieve uniform release of the entire skin edge to the desired anatomic depth and to create smooth and perpendicular wound edges without a bevel.¹³ Before beginning the procedure, the surgeon should have a clear plan for the anatomic depth of the incision. The desired anatomic depth will vary based on the location and intent of the procedure. In most cases, the depth of the incision will correspond to the intended anatomic plane for the subsequent steps of excision and undermining. The skin should be released to a uniform depth along the entire incision (Fig 3).

The incision should create wound edges that are sharply perpendicular to the skin surface, because any bevel of the dermis or fat will impede the direct apposition of the epidermal edges during suturing (Fig 4). Beveled wound edges will force the surgeon to place excessive tension on the sutures, a practice that increases the risk of leaving suture marks on



Fig 2. Suboptimal appearance of a wound 1 week postsurgery and immediately after removing the cutaneous sutures. Prominent inflammation and inversion of the wound edges have resulted from imprecise surgical technique and signal an opportunity to improve technical skills.



Fig 3. The incision should achieve uniform release to the desired anatomic depth. Note this fusiform incision where the tips have not been incised to the same depth as the sides of the specimen. The tips (*black arrowheads*) require additional release.

each side of the scar (Fig 5). The angle of the scalpel relative to the skin influences whether or not the incision creates beveled wound edges. The scalpel handle tends to fall toward the surgeon's dominant hand, similar to the eraser end of a pencil, thereby positioning the blade in an undesirable beveled position (Fig 6, A). The surgeon must compensate for this natural tendency by taking care to hold the scalpel perpendicular to the surface of the skin throughout the entire pass of the incision (Fig 6, B).

Cleanly incised wound edges facilitate precise approximation of the epidermis and dermis during suturing. Jagged wound edges complicate suturing. A sharp scalpel should incise the skin smoothly with minimal downward pressure. If the surgeon forces the scalpel with downward pressure in an attempt to reach the desired depth in 1 pass, or if the scalpel edge is dull, the scalpel may succumb to chatter, resulting in jagged wound edges. To avoid chatter,



Fig 4. Intraoperative appearance of a wound repaired with suboptimal technique. The *black arrow* indicates a prominent beveled edge of the dermis. The beveled dermis will prevent direct approximation of the wound edges, regardless of the quality of the buried sutures. In an attempt to close the gap between the epidermal edges, the superficial sutures have been placed with excessive tension. The prominent gap at the puncture site of the superficial sutures (*black arrowhead*) risks track marks.



Fig 5. Typical long-term appearance of a scar repaired with excessive tension on the superficial sutures. The scar has spread, and prominent track marks are present.

especially in thick or fibrotic skin, >1 pass of the scalpel may be necessary to reach the desired depth. If multiple passes are necessary to incise through thick skin (eg, on the back and proximal extremities), applying pressure of the scalpel against the outside wound edge can decrease the risk for a bevel on subsequent passes. Using the nondominant

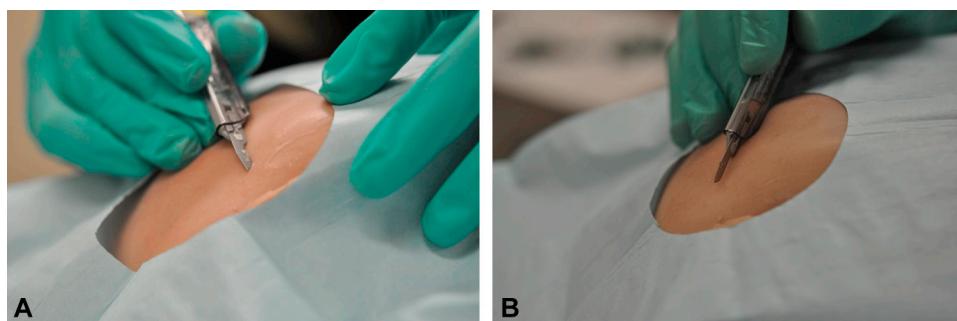


Fig 6. **A**, Suboptimal surgical technique, with the scalpel handle falling toward the dominant hand. This position predictably incises the skin with a beveled edge. **B**, Sound surgical technique, with the scalpel handle and blade held perpendicular to surface of the skin. This position will help to incise the skin with a vertical wound edge and no bevel.

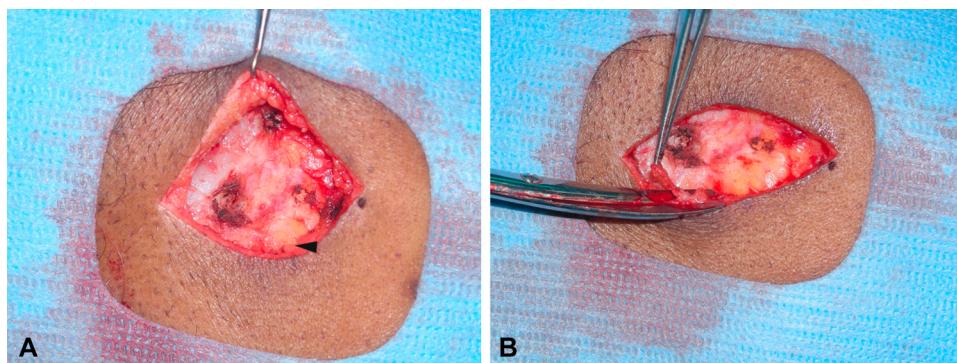


Fig 7. **A**, Intraoperative appearance of a wound after incision, excision, and undermining. The epidermis and dermis have retracted away from the center of the wound more than the subcutaneous fat. The lagging fat (*black arrowhead*) creates a beveled edge that obscures visualization of the reticular dermis and will obstruct direct approximation of the dermis. **B**, Intraoperative appearance of the same wound showing the technique of using tissue scissors to trim to the lagging fat bevel flush with the dermis. The fat bevel on the superior wound edge has already been trimmed and now has an incised wound edge with a precisely vertical face.

hand to stabilize the skin with gentle downward pressure (as opposed to lateral traction) also minimizes a beveled dermis with each pass of the scalpel.

The epidermis and dermis have greater surface tension compared to subcutaneous fat. After incising through the dermis, the epidermis and dermis immediately retract away from the incision, and the subcutaneous fat tends to lag toward the center of the wound (Fig 7, A). If the lagging fat obscures the dermis or extrudes between the wound edges during the placement of deep sutures, trimming it flush with the dermis allows for greater visibility of the reticular dermis for accurate placement of the buried dermal sutures (Fig 7, B). In many cases, this is best accomplished after undermining. Using forceps to gently stabilize the lagging fat, the surgeon can use tissue scissors to trim the fat flush with the dermis and create a sharply perpendicular wound edge along the full thickness of the skin flap. Excessive traction should be avoided, because it frequently

causes a reverse bevel (ie, a bevel away from the center of the wound), which makes it more difficult to place the deep sutures without a prominent dimple.

Goal of incision

The goal of incision is to achieve a uniform release along the entire skin edge to the desired anatomic depth and to create smooth and perpendicular wound edges with no bevel.

Quality control checkpoints for incision

1. Has the incision achieved uniform release to the desired anatomic plane?
 - a. Troubleshooting #1—If the incision has not reached the desired anatomic depth, complete the incision to get uniform release.
 - b. Troubleshooting #2—If the incision extends more deeply than the intended depth of

- the excision and undermining, be careful that the subsequent steps of excision and undermining occur in the correct anatomic plane.
2. Are the incised wound edges perpendicular without a bevel of the dermis or fat?
 - a. Troubleshooting #1—If the dermis is cut with a beveled edge, ensure that the angle of the scalpel is perpendicular to the plane of the skin throughout the entire pass of the incision (Fig 6, B).
 - b. Troubleshooting #2—If the dermis is cut with a beveled edge, assess the method of stabilizing the skin. The application of downward pressure perpendicular to the surface of the skin is less likely to produce a beveled edge compared to stretching each side of the skin away from the path of the incision.
 - c. Troubleshooting #3—To avoid a beveled dermal edge, consider using a no. 10 scalpel for anatomic locations with a thick dermis.
 - d. Troubleshooting #4—If the dermis is cut with a beveled edge, grip the redundant tissue with a forceps and apply gentle traction into the wound. Incise through the beveled dermis to create a clean and perpendicular edge.
 - e. Troubleshooting #5—If the subcutaneous fat is lagging in the center of the wound, consider using tissue scissors to trim the lagging fat flush with the vertical face of the incised dermis (Fig 7, B).
 3. Are the wound edges cut cleanly without jagged edges?
 - a. Troubleshooting #1—Jagged edges may occur from excessive downward pressure or the use of a dull scalpel. Ensure that the scalpel is sharp and pass the scalpel lightly, allowing >1 pass to achieve the desired depth, if necessary.
 - b. Troubleshooting #2—Jagged edges may occur if loose skin is not stabilized while incising. Improve stabilization of the skin while incising.
- ### Common errors to avoid during incision
1. Failure to incise to the desired anatomic depth (ie, either too superficial, leading to no release, or too deep, leading to bleeding through the gully from the incision)
 2. Holding the scalpel at an angle that creates a beveled edge
 3. Jagged wound edges resulting from chatter caused by excessive downward pressure on the scalpel, from a dull blade, or from a failure to stabilize the skin while incising

CUTTING TECHNIQUE: EXCISING

Key points

- **Excision should remove the lesion or excess skin during the reconstruction with minimal collateral damage to important anatomic structures**
- **The anatomic plane of the excision ideally corresponds to the depth of initial skin incision; otherwise, hemostasis may be more challenging or bulky soft tissue in the central wound may impede apposition of wound edges**
- **The ideal anatomic plane of excision varies by location on the body**
- **Ideal planes of excision are characterized by the effortless release of tissue and minimal bleeding**

Excision has 2 purposes: either to (1) ensure complete removal of a lesion or to (2) restore contour by removing the standing cone or excess tissue during the reconstruction. Based on the clinical examination and pathology of the preoperative biopsy specimen, the surgeon must determine the anatomic depth of the excision. The excision should remove the lesion or excess skin with minimal collateral damage to important anatomic structures. Deeply infiltrating tumors may require excision to a depth that causes predictable morbidity. For example, a tumor that invades the deep fat on the temple may require excision of the temporoparietal fascia and may sacrifice the temporal branch of the facial nerve. By contrast, the surgeon can almost always dictate the anatomic plane when excising standing cones or excess tissue during the reconstruction. The ideal anatomic planes for different anatomic locations can be found in Table I.

Ideally, the preceding incision has released the skin to the desired anatomic depth and the excision continues a clean lift of tissue in the same surgical plane. In areas with thick subcutaneous fat, a disparity between the depths of the incision and excision may create unnecessary challenges during the closure. For example, if the incision extends to the fascia, but the tissue is excised at the level of the superficial subcutaneous fat, then the island of subcutaneous fat at the base of the wound can impede advancement of the wound edges during

Table I. Ideal surgical planes for incising, excising, and undermining

Anatomic location	Preferred anatomic plane	Comments/critical structures to consider
Trunk and extremities	Junction of subcutaneous fat and deep fascia	In areas on the trunk and proximal extremities, with a thicker layer of subcutaneous fat, the ideal surgical plane is the junction between the tightly organized, compact, columnar fat lobules adherent the underside of the dermis and the underlying, looser, larger, and more disorganized fat lobules that invest and obscure the fascia
Lateral aspect of the face and neck	Junction of the subcutaneous fat and SMAS	The motor branches from the facial nerve always lie deep to the most superficial layer of SMAS (in areas where the muscles of facial expression are layered [eg, lip depressors and elevators], the motor nerves innervate the deepest muscles from their superficial surface); excision at the junction of the subcutaneous fat and SMAS will always protect the motor nerves
Central third of face and scalp	At the junction of subcutaneous fat and SMAS or deep to the muscles of the SMAS or galea (on scalp)	Because the branches of the facial nerve have arborized before reaching the central third of the face, excision deep to the SMAS is less likely to cause motor deficits (eg, excision of midline and paramedian frontalis muscle does not leave motor deficit on the forehead); on the midline nose, forehead, and scalp, undermining deep to the SMAS is frequently desirable

SMAS, Superficial musculoaponeurotic system.



Fig 8. This intraoperative photograph shows a discrepancy between the anatomic depths of the incision and excision. The incision has released to the fascia. The central island of tissue is being excised in the superficial subcutaneous fat. A gully (arrowhead) left by the deeper incision often creates challenges for hemostasis, and the central island of fat can impede advancement of the wound edges. Excising the specimen with tissue scissors reduces the likelihood of this error by providing improved tactile feedback from the release of the anatomic planes.

the closure and complicate hemostasis by obscuring blood vessels (*Fig 8*).

On the scalp, central face and temples, hands and feet, and male genitalia, the subcutaneous fat is either thin or indistinct (eg, on the mid-chin, the mentalis muscle inserts directly into the dermis and there is not a distinct layer of fat), so the surgeon encounters the underlying muscle or fascia immediately after release of the dermis. In the medial

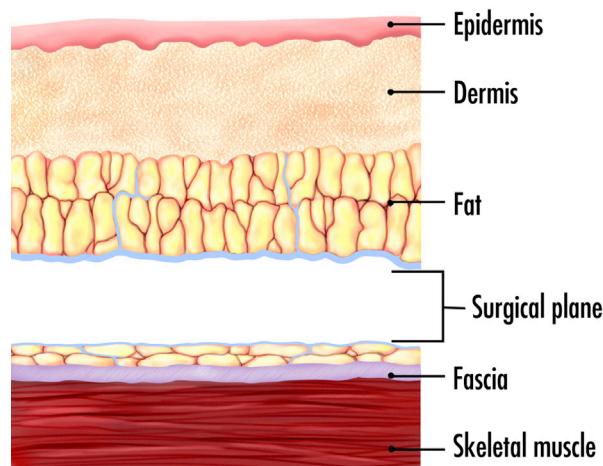


Fig 9. On the trunk and extremities, the ideal surgical plane is at the junction of the tightly organized, columnar fat adherent to the dermis and the larger, loosely organized fat lobules that invest the deep muscular fascia.

aspect of the cheek, neck, trunk, proximal extremities, and female genitalia, there is frequently a thicker layer of subcutaneous fat. In these locations, a layer of columnar, compact, and tightly organized fat lobules adheres to the underside of the dermis. A surgical plane separates these tightly organized columnar lobules from a deeper layer of larger, more loosely organized fat lobules that invest the fascia (*Fig 9*). Vigorous scrubbing with gauze can often dislodge these deeper, loosely organized, larger fat lobules from the fascia. The junction of

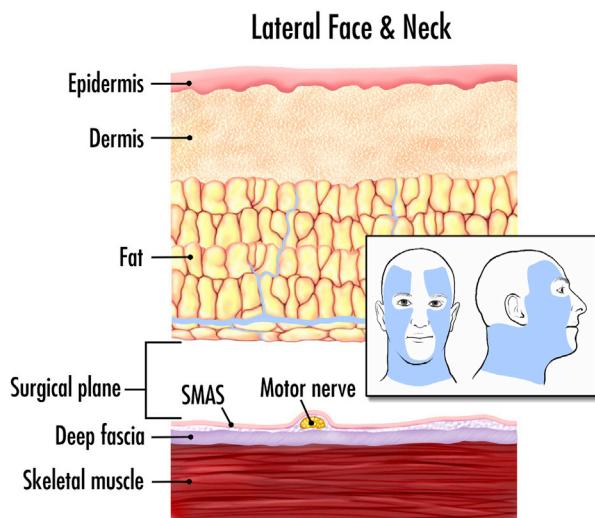


Fig 10. Excising and undermining superficial to the superficial musculoaponeurotic system of the face and investing cervical fascia of the neck preserves the underlying branches of the facial nerve on the lateral face and the spinal accessory nerve in the posterior triangle of the neck.

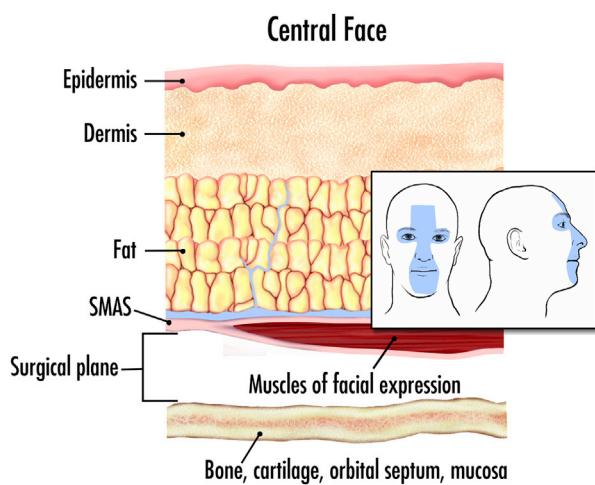


Fig 11. On the central face, where there is minimal risk for motor deficits from working in a deep surgical plane, the anatomic plane of excision is usually deep to the muscles of facial expression/superficial musculoaponeurotic system. For smaller procedures, the surgeon may choose a surgical plane superficial to the superficial musculoaponeurotic system.

these 2 layers of fat provides a natural and efficient surgical plane that releases effortlessly. Optimal planes for excision vary by location (Table 1). Excising at the junctions of tissue planes minimizes bleeding and allows for effortless dissection. On the trunk and extremities, the junction of the subcutaneous fat and deep muscular fascia provides an ideal surgical plane (Fig 9). In order to preserve the

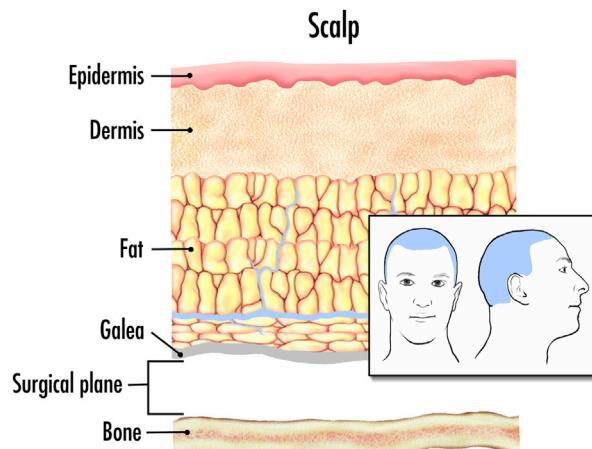


Fig 12. On the scalp, the anatomic plane of the excision is usually deep to the galea aponeurotica.

underlying branches of the facial nerve on the lateral aspect of the face and the spinal accessory nerve in the posterior triangle of the neck, the surgeon excises at the junction of the subcutaneous fat and fascia of the superficial musculoaponeurotic system (SMAS; Fig 10). On the central face, excising deep to the muscles of facial expression/SMAS poses a minimal risk for motor deficits (Fig 11). Whereas the most common surgical plane on the nose and central forehead is deep to the SMAS, it is more common to work superficial to the orbicularis oris muscle around the mouth. For smaller procedures in the central face, the surgeon may choose a surgical plane superficial to the SMAS. In the midline forehead, for example, the surgeon may choose to stay above the frontalis for a small horizontal excision in order to minimize postoperative sensory deficits, but may excise deep to the frontalis to remove bulk and facilitate tissue advancement for a large excision. On the scalp, the anatomic plane of the excision is usually deep to the galea aponeurotica (Fig 12).

The surgeon can use either scissors or a scalpel for excision. Scissors have some advantages over scalpels, especially when the surgeon does not have intimate knowledge of the surgical planes. Compared to the scalpel, scissors provide more tactile feedback, which helps the surgeon feel the release of tissue and maintain a uniform anatomic plane. Scissors should split the anatomic plane with ease, especially in healthy skin without fibrosis from a previous scar. Undue resistance during excision should prompt the surgeon to reevaluate the accuracy of the anatomic plane. In contrast to scissors, the blind, sharp edge of the scalpel more easily breaches tissue planes. Especially in areas with thick subcutaneous fat, such as the abdomen or



Fig 13. Assessing the excision specimen for uniform thickness serves as a quality control checkpoint. The fusiform excision specimen in the photograph has a uniform thickness in profile. In this case, the small excision specimen was removed in plane of the superficial subcutaneous fat. Excising the specimen at the junction of the subcutaneous fat and fascia is usually a more efficient surgical plane that allows for easier isolation of vessels for hemostasis.

proximal thigh, there is a tendency for the scalpel to cut progressively deeper during the excision and for the underside of the specimen to have scalloped incisions. The surgeon should aim for a clean separation of anatomic planes and an excision specimen with a uniform thickness in profile that reflects the accuracy of the plane of excision (Fig 13).

Goal of excision

The goal of excision is to remove the skin in a uniform and efficient anatomic plane with minimal morbidity to the underlying structures.

Quality control checkpoints for excision

1. Is the excision effortless and does it cause minimal bleeding?
 - a. Troubleshooting—Undue resistance or excessive and diffuse bleeding from small vessels frequently signifies an inefficient plane of excision. Reevaluate the plane of excision and aim for the junction of tissue planes, where excision usually occurs effortlessly and with less bleeding (Figs 9-12).
2. Does the excision specimen have a uniform thickness (Fig 13)?
 - a. Troubleshooting—if the profile view of the excised specimen has varying thicknesses, then consider using scissors, rather than a scalpel, to gain the tactile feedback that helps maintain a uniform anatomic plane during excision.



Fig 14. Examining the base of the wound for a uniform surgical plane serves as a quality control checkpoint. The plane of excision on the anterior surface of the neck seen in this photograph is immediately superficial to the platysma muscle, providing a relatively bloodless and efficient surgical plane.

3. Does the base of the wound have a uniform depth at the desired anatomic plane (Fig 14)?
 - a. Troubleshooting—if the base of the wound does not have a uniform anatomic depth because of a partially shallow excision, then complete the excision of the remaining superficial tissue to the desired anatomic plane. If portions of the wound have been excised more deeply than the preferred anatomic depth, be careful that undermining occurs more superficially at the preferred anatomic plane.

Common errors to avoid during excision

1. Failure to excise the specimen in a uniform anatomic plane
2. Mismatch between the anatomic depths of the incision and excision
3. Failure to excise the tissue at the junction of tissue planes

CUTTING TECHNIQUE: UNDERMINING

Key points

- Undermining may facilitate advancement of the wound edges and eversion when suturing
- Wounds at anatomic sites where the fascia is adherent to the overlying dermis benefit most from undermining
- Excessive undermining can threaten the blood supply of the flap and rarely provides a mechanical advantage
- The plane of undermining frequently corresponds to the plane of excision

- **An efficient plane of undermining is characterized by effortless release of the tissue and minimal bleeding**
- **Efficient undermining requires effective countertraction, most frequently applied with a skin hook, directly over the point of release**

The goals of undermining are to (1) facilitate tissue advancement by releasing either the skin edges or flap from underlying adhesions and to (2) facilitate eversion of the wound edges during suturing. The surgeon must make 2 key decisions when undermining: (1) the ideal anatomic plane for undermining and (2) the extent of undermining (ie, how widely to undermine). In most cases, the anatomic plane for undermining coincides with the depth of the incision and the plane of the excision.

If the surgeon is working in an efficient surgical plane, undermining should occur with ease. Undue resistance while undermining usually signifies an inefficient anatomic plane (eg, most commonly splitting the subcutaneous fat rather than working at the junction of the fat and fascia). The ideal surgical plane varies based on the location (Table I and Figs 9–12). In some instances, undermining at a more superficial anatomic depth than the excision can minimize morbidity. For example, if excision of the temporoparietal fascia is necessary to clear a tumor on the temple, the surgeon may decrease morbidity to the underlying temporal branches of the facial nerve by undermining the edges of the reconstruction superficial to the temporoparietal fascia.

The extent of undermining varies according to the procedure. For primary closures, wide undermining rarely increases mobility of the skin edges. Minimal undermining (ie, 0.5–1.0 cm) will usually suffice. For deep wounds or very loose skin (eg, on the forearm or lateral aspect of the neck), undermining may not be necessary. Fascial plication sutures can advance tissue and decrease undermining requirements.¹⁴ To decide whether undermining is necessary, the surgeon can use a skin hook to pull the incised wound edge to its desired position. If underlying adhesions restrict mobility or fix the skin in an inverted position, undermining will help. Undermining is most beneficial in areas where the fascia and the underlying dermis have dense connections (eg, the muscles of facial expression inserting in the dermis at the apical triangle of the lip).

Undermining influences the vascular supply and mobility of the flap. The vascular supply to the flap varies according to anatomic plane and the extent of undermining. Flaps elevated too superficially (eg, immediately subdermal) may not have adequate



Fig 15. Sharp undermining improves operative efficiency. When working in efficient surgical planes, sharp undermining occurs with ease. This photograph shows the practice of sliding 1 blade of the tissue scissors in the desired surgical plane, then using the second blade to complete the release. Using this slide and divide technique of undermining, the surgeon does not have to rediscover the preferred undermining plane with each new cut.

blood supply.¹⁵ To optimize blood supply, local flaps should contain at least the epidermis, dermis, and the tight columnar cells of subcutaneous fat immediately adherent to the dermis (Fig 9). Undermining deep to muscle or fascia improves flap blood supply but may increase morbidity, depending on the anatomic location of the surgery (Table I). For example, in the central face (eg, the nose and central forehead) and scalp, undermining deep to the muscles of facial expression or galea, respectively, is desirable in most cases (Figs 11 and 12). By contrast, on the lateral aspect of the face, temple, and posterior triangle of the neck, undermining superficial to the SMAS and investing fascia of the neck, respectively, preserves function of the underlying motor nerves (Fig 10).

Undermining too widely can threaten a flap's blood supply or increase the possibility of postoperative bleeding and hematoma formation.^{16–18} In general, the surgeon should aim to undermine just enough to move the flap into place. Frequent assessment of skin edge mobility while undermining helps to avoid unnecessarily wide undermining. When the skin edges comfortably stretch to their desired target, additional undermining is rarely helpful or necessary.

Sharp undermining improves efficiency. With a thorough knowledge of anatomy, the surgeon can undermine sharply and with confidence. Compared to the scalpel, scissors allow sharp undermining with better tactile feedback. The scissors precisely release the skin at the desired surgical plane. After the initial releasing cut, the surgeon can efficiently undermine the remaining skin by sliding 1 blade of the scissors in the newly released space and by using the second blade to complete the cut (Fig 15). Using this slide



Fig 16. The wound edges have been undermined in the same surgical plane as the base of the excision. In this case on the temple, the surgical plane is at the junction of the subcutaneous fat and the superficial musculopaponeurotic system.

and divide technique,^{19,20} the surgeon does not have to rediscover the preferred undermining plane with each new cut. Blunt undermining may be preferred where fascial planes are being separated, such as on the dorsal surface of the hand or under the galea of the scalp. These avascular planes may be split simply by inserting the closed tips of the scissors in the desired plane of undermining then spreading the instrument.

Countertraction with skin hooks greatly facilitates undermining. Compared to forceps, skin hooks allow forceful countertraction of the skin without epidermal trauma. The skin hook should be placed firmly at the desired depth of undermining (usually firmly under the dermis) immediately over the point of undermining. If the skin hook is placed too superficially (eg, in the mid-dermis), the instrument tends to slip from the skin. If the skin hook is placed remotely from the point of undermining with the scissors, the forces of countertraction diminish and undermining is more difficult. Therefore, as the scissors progress to a new spot, the retracting skin hook should follow. When undermining is complete, there is often a bevel of subcutaneous fat along the incised face of the skin edge. Tissue scissors can be used to trim this fat bevel flush with the dermis (Fig 7, B).

Goal of undermining

The goal of undermining is to facilitate advancement of skin edges by releasing the skin edges from underlying adhesions and to facilitate eversion of the wound edges during suturing.

Quality control checkpoints for undermining

1. Is undermining effortless, and does it cause minimal bleeding?

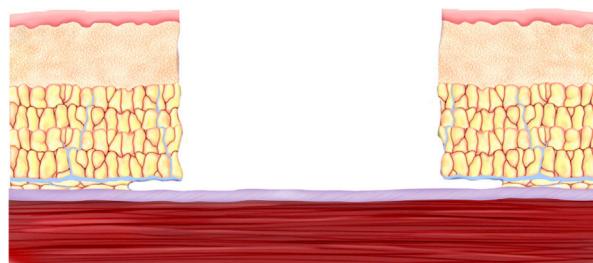


Fig 17. Upon final inspection from the cutting steps, the surgeon should observe a wound with cleanly incised, vertical wound edges, a wound base uniformly located at the preferred anatomic plane, and skin flaps undermined enough to allow advancement and eversion of the wound edges.

- a. Troubleshooting #1—If undermining is difficult, reassess the surgical plane (Table 1). Resistance during undermining frequently occurs from working in a suboptimal surgical plane.
- b. Troubleshooting #2—If undermining is difficult, evaluate whether countertraction was performed effectively. Efficient undermining requires forceful countertraction directly over the point release. Undermining will feel difficult if countertraction is either absent or remote from the exact point of undermining.
2. Can the incised skin edge be retracted in an everted position?
 - a. Troubleshooting—If a skin hook cannot retract the skin edge in an everted position, then connective tissue adhesions will likely force the wound edge in an inverted position. The wound edge may need additional undermining before suturing. Wide undermining rarely facilitates eversion.
3. Are the wound edges sharply perpendicular from the epidermis to the plane of undermining?
 - b. Troubleshooting—After undermining, there is often a bevel of subcutaneous fat along the incised face of the skin edge. Tissue scissors can be used to trim this fat bevel flush with the dermis (Fig 7, B).

Common errors in undermining

1. Undermining in a suboptimal surgical plane
2. Undermining without effective countertraction
3. Insufficient undermining that restricts eversion of the incised wound edge
4. Failure to trim the fat bevel to create sharply perpendicular wound edges after undermining

CONCLUSION

The initial steps to cutaneous surgery require cutting, including incising, excising, and undermining. After the cutting steps, the ideal wound has cleanly incised, vertical wound edges, a base at a uniform anatomic plane, and precisely undermined skin edges (Figs 16 and 17). Part I of this continuing medical education article provided quality control checkpoints and troubleshooting solutions to address common challenges during incision, excision, and undermining to help surgeons create wounds ideally suited for repair with precise and efficient buried and superficial sutures.

REFERENCES

- Burget GC, Menick FJ. Aesthetic reconstruction of the nose. St Louis: Mosby; 1994.
- Robinson JK. Segmental reconstruction of the face. *Dermatol Surg*. 2004;30:67-74.
- Peyre SE, Peyre CG, Sullivan ME, Towfigh S. A surgical skills elective can improve student confidence prior to internship. *J Surg Res*. 2006;133:11-15.
- Graziano SC. Randomized surgical training for medical students: resident versus peer-led teaching. *Am J Obstet Gynecol*. 2011;204:542.e1-e4.
- Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511-520.
- Gawande AA. Personal best: top athletes and singers have coaches. Should you? Available at: <http://www.newyorker.com/magazine/2011/10/03/personal-best>. Accessed January 8, 2015.
- Singer AJ, Arora B, Dagum A, Valentine S, Hollander JE. Development and validation of a novel scar evaluation scale. *Plast Reconstr Surg*. 2007;120:1892-1897.
- Verhaegen PD, van der Wal MB, Middelkoop E, van Zuijlen PP. Objective scar assessment tools: a clinimetric appraisal. *Plast Reconstr Surg*. 2011;127:1561-1570.
- Bloemen MC, van Gerven MS, van der Wal MB, Verhaegen PD, Middelkoop E. An objective device for measuring surface roughness of skin and scars. *J Am Acad Dermatol*. 2011;64:706-715.
- Ogawa R. Mechanobiology of scarring. *Wound Repair Regen*. 2011;19(suppl 1):S2-S9.
- Ogawa R, Akaishi S, Huang C, et al. Clinical applications of basic research that shows reducing skin tension could prevent and treat abnormal scarring: the importance of fascial/subcutaneous tensile reduction sutures and flap surgery for keloid and hypertrophic scar reconstruction. *J Nippon Med Sch*. 2011;78:68-76.
- Martin D, Umraw N, Gomez M, Cartotto R. Changes in subjective vs objective burn scar assessment over time: does the patient agree with what we think? *J Burn Care Rehabil*. 2003;24:239-244.
- Zitelli JA. TIPS for a better ellipse. *J Am Acad Dermatol*. 1990; 22:101-103.
- Kantor J. The fascial plication suture: an adjunct to layered wound closure. *Arch Dermatol*. 2009;145:1454-1456.
- Pearl RM, Johnson D. The vascular supply to the skin: an anatomical and physiological reappraisal—part I. *Ann Plast Surg*. 1983;11:99-105.
- Daniel RKC. The anatomy and hemodynamics of the cutaneous circulation and their influence on skin flap design. Boston: Little, Brown, & Co; 1975.
- Cutting C. Critical closing and perfusion pressures in flap survival. *Ann Plast Surg*. 1982;9:524.
- Cutting C, Ballantyne D, Shaw W, Converse JM. Critical closing pressure, local perfusion pressure, and the failing skin flap. *Ann Plast Surg*. 1982;8:504-509.
- Zitelli JA, Moy RL. Buried vertical mattress suture. *J Dermatol Surg Oncol*. 1989;15:17-19.
- Boyer JD, Zitelli JA, Brodland DG. Undermining in cutaneous surgery. *Dermatol Surg*. 2001;27:75-78.

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Surgical technique for optimal outcomes

Part II. Repairing tissue: Suturing

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Learning objectives

After completing this learning activity, participants should be able to describe common suturing errors that lead to unaesthetic scars and identify methods to gain hemostasis efficiently and re-approximate skin in a layered fashion with proficiency.

Disclosures

Editors

The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

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Sound surgical technique is necessary to achieve excellent surgical outcomes. Despite the fact that dermatologists perform more office-based cutaneous surgery than any other specialty, few dermatologists have opportunities for practical instruction to improve surgical technique after residency and fellowship. This 2-part continuing medical education article will address key principles of surgical technique at each step of cutaneous reconstruction. Part II reviews the placement of deep and superficial sutures. Objective quality control questions are proposed to provide a framework for self-assessment and continuous quality improvement. (*J Am Acad Dermatol* 2015;72:389-402.)

Key words: excise; excision; incise; skin; surgery; suture; technique; undermine.

INTRODUCTION

Part I of this continuing medical education article reviewed surgical techniques that involve cutting tissue: incising, excising, and undermining. Final inspection of the wound after completing these cutting steps should reveal cleanly incised, vertical wound edges, a wound base with a uniform anatomic depth, and precisely undermined skin flaps. Careful hemostasis should minimize bleeding. Strategies for effective hemostasis have been reviewed elsewhere.^{1,2} Precise execution of these cutting steps prepares the wound for accurate placement of buried and superficial sutures.

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REPAIRING TISSUE: PLACING BURIED SUTURES

Key points

- The preferred caliber of the suture and size of the needle depend on the anatomic location, thickness of the skin, and tension of the wound
- Suture sequence and surgeon positioning influence the efficiency and execution of subcutaneous sutures
- The proper placement of buried vertical mattress sutures and atraumatic handling of skin are critical steps that achieve optimal surgical outcomes

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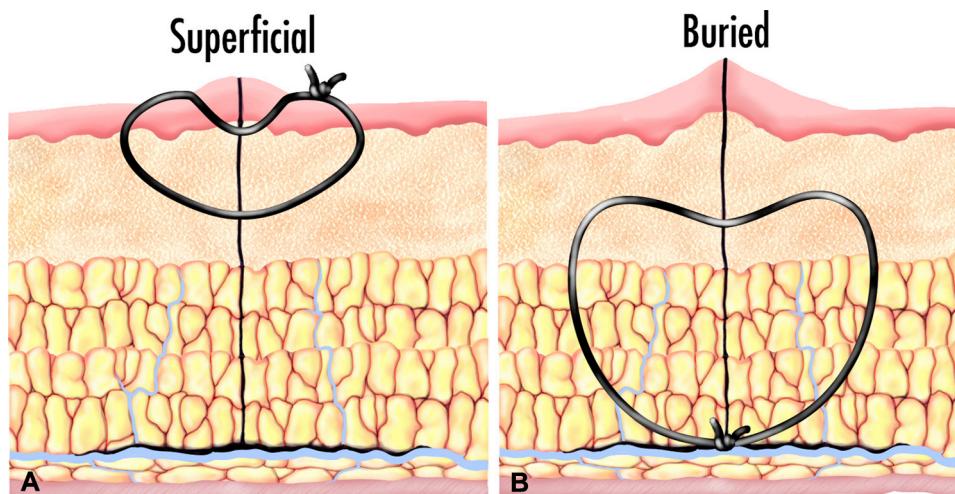


Fig 1. The superficial (A) and buried vertical mattress (B) sutures each have heart-shaped loops, but the knot is at the bottom of the loop for the buried suture.

- **The buried vertical mattress suture everts the wound edges and allows for tension-free approximation of the papillary dermis and epidermis**
- **After the effective placement of buried vertical mattress sutures, both wound edges should be clearly visible and there should be minimal bleeding from exposed dermis**

The anatomic layers requiring suturing will vary by site, depth, and wound complexity.³ This article will focus on the most common wounds in cutaneous surgery: wounds that extend through the epidermis, dermis, and subcutaneous fat. Buried or subcutaneous sutures eliminate dead space, approximate the dermis and epidermis, and provide strength to the wound as the scar matures. The buried vertical mattress suture is the workhorse for deep sutures and will be the primary technique discussed herein.⁴ It creates the same heart-shaped loop as a superficial vertical mattress suture, except that the knot lies at the bottom of the loop (Fig 1). Numerous other techniques for buried sutures may also accomplish the accurate approximation of wound edges; however, a comprehensive discussion of these lies beyond the scope of this article.⁵ Judicious selection of the suture and needle, a thoughtful plan for suture sequence, and positioning relative to the wound are the first steps for effective execution of the buried vertical mattress suture.

The material and caliber of the suture and the type and size of the needle influence execution of the buried vertical mattress suture. Previous articles and educational resources provide a comprehensive review of suture materials.^{5,6} In most cases, a dissolving rather than a permanent suture is ideal for buried sutures. Slowly absorbing intradermal

sutures, such as polydioxanone, may decrease scar spread in high tension wounds.⁷ Wound tension determines the ideal size of the suture. High-tension wounds (eg, those on the torso or proximal extremities) may require a 3-0 or 2-0 suture. In moderate tension wounds, a 4-0 suture may provide sufficient strength. For wounds under minimal tension, a 5-0 suture will usually suffice. In general, using the smallest caliber suture that provides sufficient tensile strength is desirable to minimize the amount of suture material in the wound. The type and size of the suture needle strongly influence execution of deep sutures. Most surgeons prefer to place deep sutures with a reverse cutting needle. The choice of needle size depends primarily on the thickness of the dermis; in anatomic areas with a thin dermis, a smaller needle is required, such as a 3/8 arc P-3 needle. Anatomic areas with a thicker dermis require a larger needle, such as a 3/8 arc PS-2 needle. In locations with thick skin, such as the back, a half-circle reverse-cutting needle may facilitate placement of the buried vertical mattress suture. Using a large needle in anatomic areas with a thin dermis will risk tearing the skin. Using a small needle in anatomic areas with a thick dermis frequently leads to bent needles as the surgeon struggles to rotate the needle far enough to retrieve the tip.

Suture sequence influences operative efficiency and execution. Placing deep sutures is more challenging in areas of high versus low tension.⁸ The strategy of placing the first sutures in the area of highest tension then moving to areas of progressively lower tension has its advantages. First, access and visibility to the areas of greatest tension are easiest before most of the wound has been closed. The alternative strategy of placing the

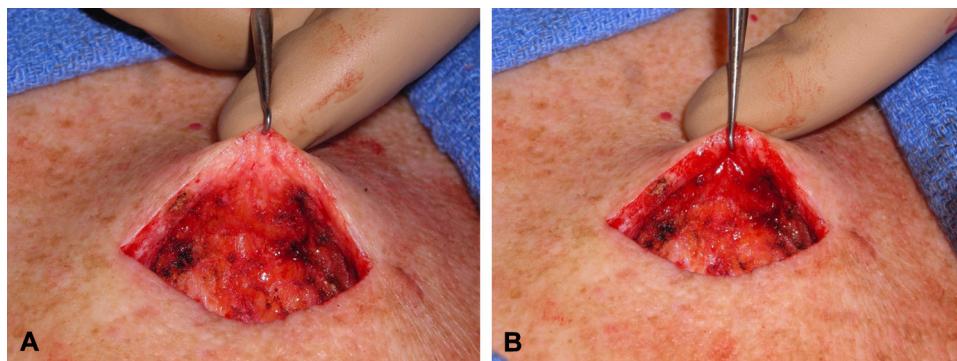


Fig 2. Countertraction with either forceps or a skin hook exposes the dermis for placement of the deep sutures. **A**, Ideal placement of the retracting instrument in the papillary dermis maximizes visibility of the dermis and orients the skin in an everted position. **B**, Suboptimal placement of the retracting instrument in the reticular dermis compresses the dermis, which minimizes visibility and orients the skin in an inverted position.

initial sutures at the areas of lowest tension may leave a smaller space to throw the sutures in the areas of greatest tension, which often results in bent needles, difficulty retrieving the tip of the needle from the center of the wound, an inability to access the deepest anatomic layers of the wound, and increased trauma and tearing of the skin. A second advantage of placing the initial sutures in the areas of greatest tension is that it provides time for tissue creep, if complete closure with the initial suture is not possible.^{9,10} The first deep suture should be cinched as much as the tension of the wound edges will allow. When complete apposition is not possible initially, the surgeon can continue suturing in areas with less tension. By the time the areas with less tension have been sutured, tissue creep may allow the surgeon to return and completely close the area with greatest tension. In many instances, the surgeon may first suture areas of the wound with less tension. Whatever the suture sequence, the surgeon will benefit from leaving sufficient space and easy access for accurate and efficient placement of sutures in the most critical, high-tension areas.

The position of the surgeon relative to the wound also influences the efficiency and execution of buried sutures. In general, it is easier to throw a buried suture when the dominant hand lies on the side of the wound where the skin is looser. When loaded into the needle driver, the shank of the suture needle (ie, the portion closest to the suture) usually points to the dominant, throwing hand of the surgeon. In tight spaces, the shank of the needle can impede the execution of deep sutures. If the surgeon positions him or herself so that the shank of the needle and dominant hand are on the same side as the looser wound edges, the surgeon can retract the loose skin to allow easier passage of the needle.

Countertraction to evert the skin edge with either the forceps or skin hook is essential for efficient and accurate execution of the buried vertical mattress suture. The skin hook has the advantage of allowing retraction close to the epidermis with minimal to no trauma, but it requires frequent manipulation of a sharp instrument.¹¹ Some surgeons prefer to work with a double- rather than single-pronged skin hook in order to reduce the risk of sharps injury and still maintain the benefit of atraumatic tissue handling. By contrast, forceps have a higher risk of trauma to the patient's skin but allow less exposure to sharps. Both instruments can be used effectively, and the surgeon must learn to balance safety with atraumatic handling of the skin. Countertraction should occur as close to the epidermis as possible, in order to evert the skin edge and to maximize visibility of the dermis (Fig 2, A). If the instrument is placed too deeply, it compresses the dermis and orients the skin edge in an inverted position (Fig 2, B). Compression of the dermis reduces the size of the target for the deep suture, and the deep suture tends to fix the skin in an inverted position (Fig 3).

"Eversion" is defined as upward sloping skin edges that meet perfectly at the peak without any plateau or inversion. The buried vertical mattress suture facilitates eversion, which helps to counteract the contractile forces during wound healing, resists inversion of the scar, and transfers tension to the reticular dermis so that the papillary dermis and epidermis meet with minimal to no tension.¹² The buried vertical mattress suture has a heart-shaped loop with 2 peaks at the level of the mid dermis or deep papillary dermis and a valley at the level of the deep reticular dermis (Fig 1). As the difference in depth between the peaks and valley of the suture path increases, the degree of eversion will increase.

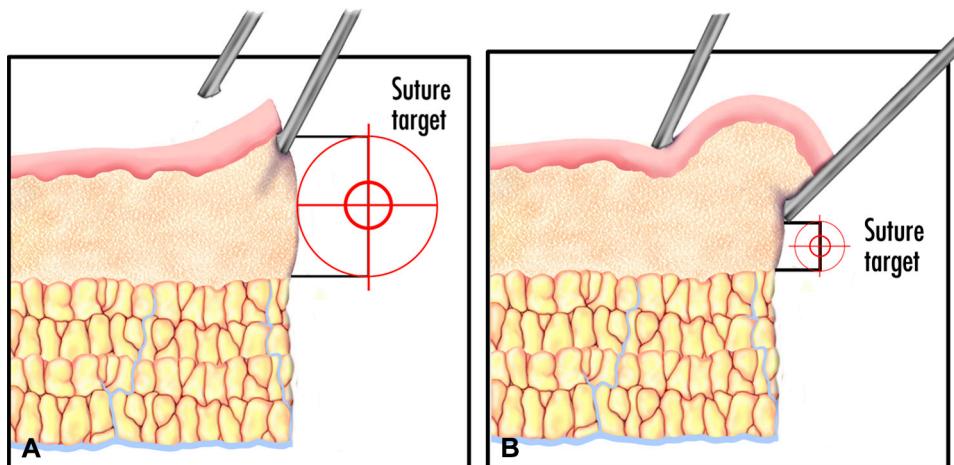


Fig 3. Schematic representation of the influence of countertraction on visibility of the dermis and position of the skin edge. **A**, Placement of the retracting instrument in the papillary dermis everts the wound edge and maximizes visibility of the dermis, providing a larger target for the deep suture. **B**, Placement of the retracting instrument in the reticular dermis inverts the wound edge and compresses the dermis, shrinking the target for the deep suture.

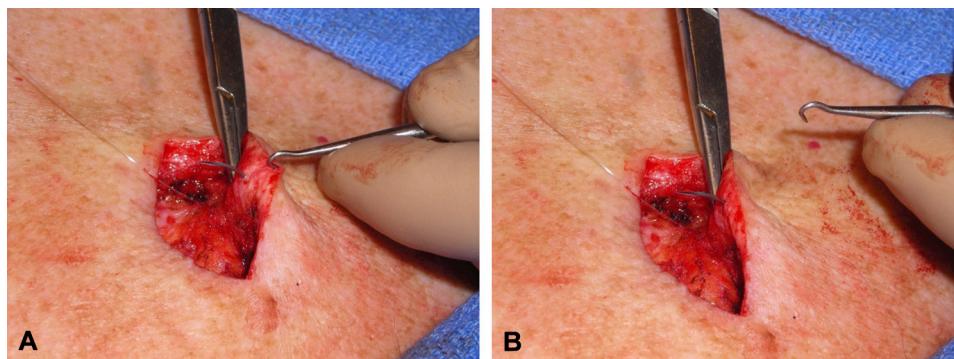


Fig 4. The “snap” of the wound edge toward the center of the wound after the first bite of the suture indicates a good path of the buried vertical mattress suture. **A**, The first bite of the suture has been completed and the skin hook still applies countertraction. **B**, The skin hook has been released and the skin edge “snaps” back toward the center of the wound.

To initiate a buried vertical mattress suture, the needle is passed starting from the base of the wound to the desired location of the peak of the heart-shaped loop. Once the tip of the needle reaches its peak at the mid dermis or papillary dermis, the needle is rotated toward the incised wound edge. During this maneuver, the wound edge must be retracted aggressively in an everted position. This will ensure that the tip of the needle will reach the incised wound edge at a greater depth, usually in the reticular dermis. When the peaks lie closer to the underside of the epidermis than the valley of the heart-shaped loop, the epidermis and papillary dermis of the incised wound edge naturally snap back toward the center of the wound upon release of the retracting forceps or skin hook (Fig 4). If the “snap” does not occur,

then there is a high likelihood of a gap between the wound edges. The needle is then passed in the opposite side of the wound to create a mirror image of the first side (Fig 5). The needle enters the wound in the deep reticular dermis and must aim to create a peak of the heart-shaped loop in the more superficial dermis. Extending the wrist will aim the needle upward. Once the tip of the needle reaches the peak, the needle is rotated toward the base of the wound. Retracting the skin edge in an everted position with the skin hook or forceps naturally facilitates the proper suture path. When the suture paths on each side are not mirror images, the wound edges will not appose each other precisely.¹² As a rule, the side with the more superficial bite of suture relative to the epidermis will have a wound edge that is depressed compared to the other side (Fig 6).

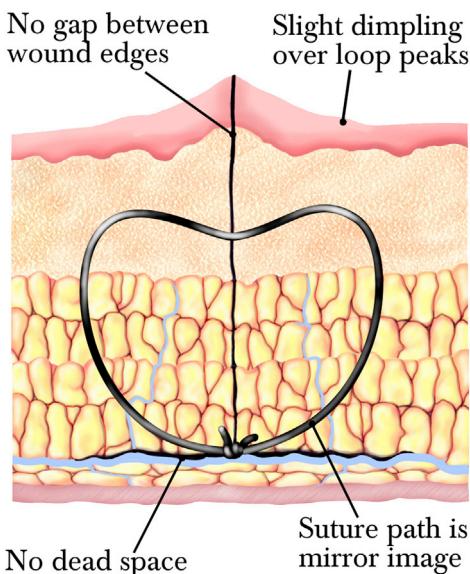


Fig 5. To achieve perfect apposition of the wound edges, each side of the completed buried vertical mattress suture should be a mirror image.

The path of the buried vertical mattress suture will vary based on the thickness of the dermis. In areas with thicker dermis (eg, the back or proximal extremities), the path of the suture must have a greater difference in height between the peaks and valley of the buried vertical mattress suture (Fig 7, A). To achieve this greater difference, the surgeon must take a wider bite (ie, further from the incised wound edge) with the skin edge retracted aggressively in an everted position. In practice, a wide bite with the skin edge retracted aggressively feels like the suture needle is passing parallel to the underside of the epidermis for as long as possible. In areas with thinner dermis (eg, eyelid and dorsal surfaces of the hand and forearm), the ideal difference in height between the peaks and valley of the buried vertical mattress sutures is smaller (Fig 7, B). To achieve this minimal difference, the surgeon must take a narrow bite (ie, closer to the incised wound edge) with the skin edge retracted in a less aggressive everted position. In practice, a narrow bite with a gently retracted everted edge feels like the suture needle is passing parallel to the vertical face of the incised skin edge. Another way to describe the difference in the suture path for thick versus thin dermis is to conceptualize the distance of the peaks of the heart-shaped loop from the incised wound edge. In thick dermis, the peaks of the heart-shaped loop will lie further from the incised wound edge and the path of the suture creates a broad based, heart-shaped loop. In thin dermis, the peaks of the heart shaped loop lie closer to the incised wound

edge and the path of the suture creates a narrow, tall, heart-shaped loop.

The suture is now ready to be tied with the knot buried at the depth of the undermined plane. An effective instrument tie prevents an “air knot” and ensures snug approximation of the wound edges.^{13,14} The running end of the suture (needle-end) is pulled so that only a few centimeters of the trailing end remain exposed on the opposite side of the wound. Each end of the suture should lie on the same side of the loop of the buried vertical mattress suture. The ends of the suture will form a V that points to the center of the wound, and the needle holder will remain between both arms of the V during knot tying. With the nondominant hand, wrap the needle end of the suture once or twice around the needle holder toward the opposite side of the wound. Grasp the trailing end of the suture with the needle holder and pull it parallel to the long axis of the wound toward the same side that the suture ends initially lay relative to the loop of the buried vertical mattress suture (video available online at www.jaad.org).¹⁵ Bring the needle holder back to center. To cinch the suture with a slip knot, throw another loop around the needle holder and pull the suture in the same direction as the first throw. To lock the knot, throw another loop with the needle holder and pull the hands in the opposite direction. The number of throws made by the surgeon will be influenced by the knot security of the suture and the tension on the wound.

To ensure an adequate number of buried sutures, the surgeon can apply the “pull test.” By pulling the wound edges away from each other, the surgeon identifies gaps that would benefit from additional buried dermal sutures. The buried sutures should support the dermis along the entire wound and still allow easy manipulation of the epidermal edges (Fig 8). If the buried sutures have been placed at an ideal depth, the surgeon can use the skin hook or forceps to retract the epidermis and papillary dermis immediately above the buried sutures. If the wound edges are firmly fixed above the buried suture, then it may have been placed too superficially.

Two quality control questions allow objective assessment of buried suture technique. First, is blood visible between the edges? Assuming effective hemostasis in the deep aspects of the wound, visible blood between the wound edges arises when the papillary dermis is either poorly approximated or frankly exposed. Second, are both wound edges clearly visible? If both wound edges are not clearly visible, then 1 edge is riding over the other like a shingle on a roof. Accurately placed buried vertical mattress sutures approximate the wound edges so

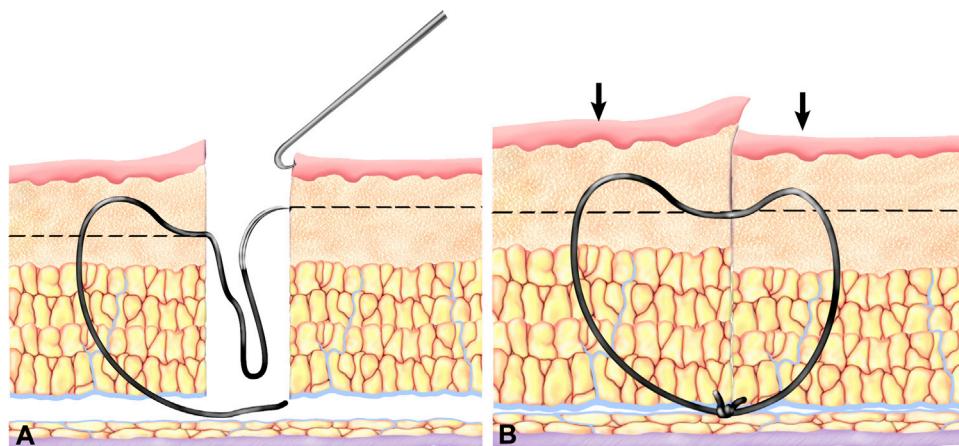


Fig 6. When the paths of the suture on each wound edge are not mirror images, a discrepancy in the height of the wound edges results. **A**, The exit point of the suture on the left side of the wound is in the reticular dermis, but the needle is entering in the papillary dermis on the right side of the wound. **B**, The right side of the wound has been pulled down by the superficial bite. The exposed dermis on the high side frequently bleeds.

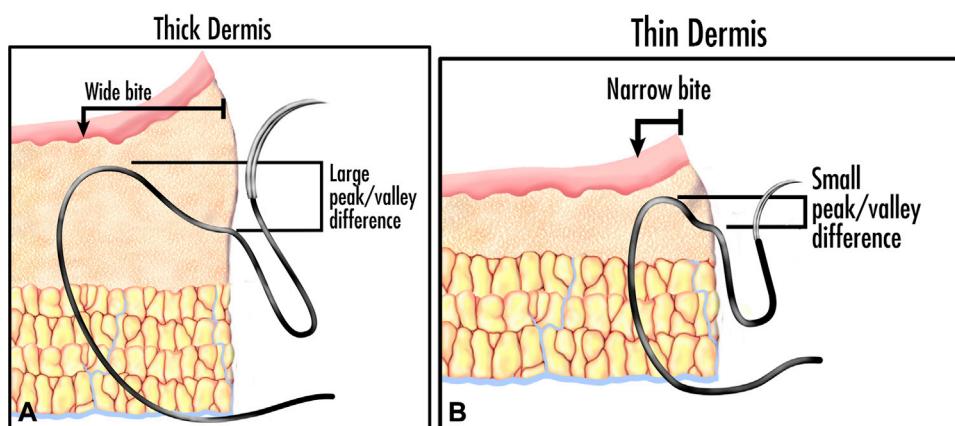


Fig 7. The path of the buried vertical mattress suture varies depending on the thickness of the dermis. **A**, Thicker dermis requires a wider bite that extends further from the incised wound edge and has a greater difference in height between the peak and valley of the heart-shaped loop. **B**, Thinner dermis requires a narrower bite with a smaller difference in height between the peak and valley of the heart-shaped loop.

precisely that bleeding between the wound edges is minimal and both wound edges are clearly visible. These 2 quality control questions help to identify several technical problems, which are addressed in the troubleshooting section, but first we will examine in detail 3 common suboptimal suture paths.

The first quality control question helps to identify 2 buried suture paths that fail to approximate the wound edges and result in bleeding from the exposed dermis. One common inefficient buried suture has a circular path, which results in flat (ie, noneverted) wound edges, with a gap between the epidermis and papillary dermis. This result occurs most frequently in areas with thick dermis and/or in wounds with excessive tension. A circular

path of the buried suture creates splayed wound edges with minimal to no eversion and lack the dimple often seen with a heart-shaped buried vertical mattress suture (Fig 9, A). The circular suture path occurs most commonly as a result of either too narrow a bite of the buried suture or failure to retract the skin edge in an everted position during the throw of the suture. A buried suture with a circular path will approximate the dermis only up to the most superficial point of the loop (Fig 9, B). Superficial to the loop, the wound edges splay away from each other. Troubleshooting requires removal of the initial deep sutures and replacement with buried vertical mattress sutures that have a wider bite and bigger difference between the distance of the peaks and

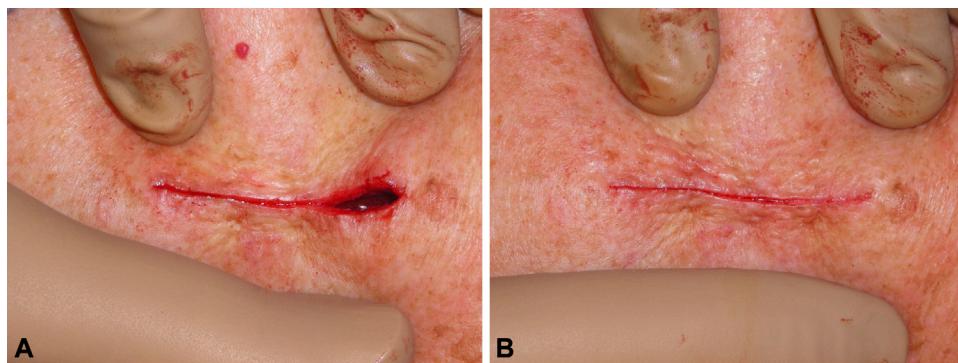


Fig 8. The “pull test” identifies wound edges that will benefit from a dermal suture. **A**, Pulling the wound edges identifies a gap remaining on the right side of the wound. **B**, After placement of another deep suture on the right side, the pull test no longer creates a gap, indicating that a sufficient number of deep sutures have been placed.

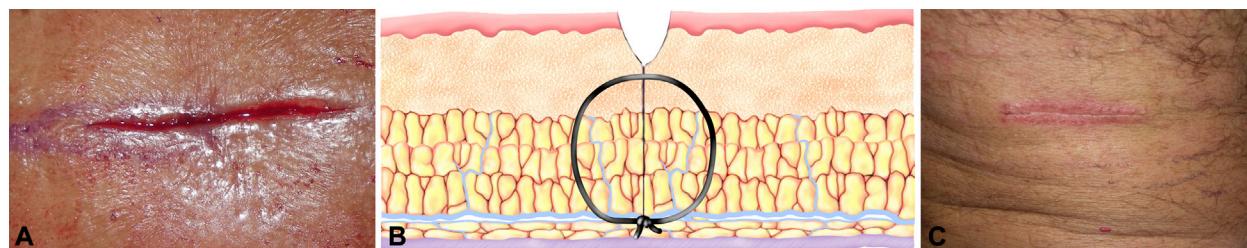


Fig 9. **A**, After placement of the deep sutures in a location with thick dermis, a gap persists between the wound edges. Note the absence of eversion. **B**, Narrow suture bites and a circular path results in a gap after the deep sutures. The wound edges with this suture path do not snap toward the center of the wound. **C**, Typical appearance of a wound 1 week postoperatively after closure with this type of deep suture. The scar is already inverted and excessive tension from the top sutures has caused intense inflammation and early track marks.

valley from the underside of the epidermis. The hallmark of this correction will be the characteristic “snap” of the wound edges toward each other and possibly a dimple of the epidermis over the peaks of the heart-shaped loop. Failure to correct this problem will result in inverted scars and undue tension on the cuticular sutures, increasing the risk for track marks (Fig 9, C).

A second pattern of buried suture that predictably results in visible blood between the wound edges is a buried vertical mattress suture that is placed too deeply. The consequent degree of eversion can be so great that approximation of the epidermal edges is not possible. Again, this result occurs most frequently in areas with thick dermis. In this extreme scenario, the undersides of the dermis are effectively sewn together and the epidermal edges cannot reach each other (Fig 10, A). The cause of this phenomenon is an excessively wide and deep bite of the buried vertical mattress suture (ie, a broad heart-shaped loop), which results in a prominent dimple far from the wound edge and excessive eversion (Fig

10, B). The correction for this phenomenon is usually replacement of the deep sutures with buried vertical mattress sutures that have a more narrow and superficial bite. Once again, the hallmark of this correction will be the characteristic “snap” of the wound edges toward each other. However, if the exposed dermis is minimal, it may be possible to trim the splayed dermis and approximate the edges without replacing the buried sutures. Failure to correct this issue before placing cutaneous sutures will result in a broad scar (Fig 10, C).

The second quality control question (ie, are both wound edges clearly visible?) identifies a suture path that occurs most commonly in skin with thin dermis. To avoid tearing of thin dermis, it is often necessary to throw the buried vertical mattress suture with a wide bite that places the peak of the heart-shaped loop too far from the wound edge (ie, the heart-shaped loop is too broad). The thin dermis cannot support an upward slope to its peak, and the everted skin plateaus or inverts when the dermis collapses (Fig 11, A). This eversion–inversion

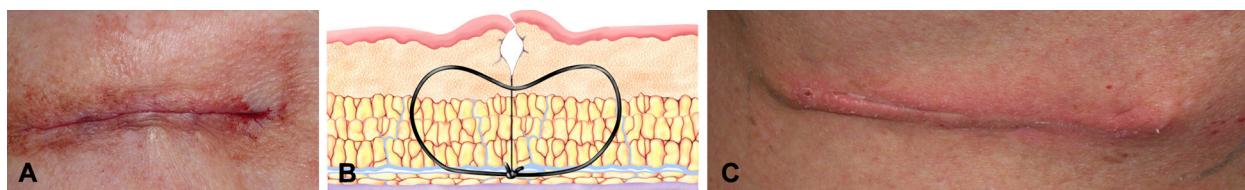


Fig 10. **A**, Appearance of a wound after deep sutures that caused eversion and inversion. The weak dermis could not support the upward slope of the wound edges, which collapsed and inverted. **B**, Everted wound edges that collapse and invert because the dermis cannot support the upward slope to a peak. The wound edge on the right rides over the left side like shingles on a roof. **C**, Two-week postoperative appearance of a wound that was sutured with collapse of eversion. The lower wound edge remains fixed over the upper wound edge, especially on the left half of the wound.

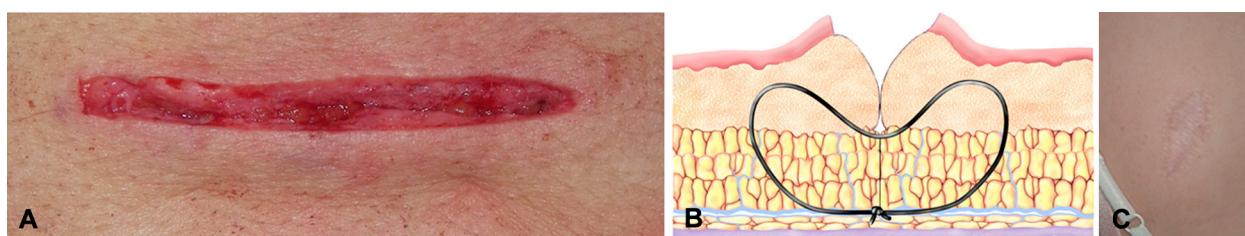


Fig 11. **A**, Excessive wound eversion has resulted in a persistent gap between the epidermal edges after placement of the deep sutures. **B**, A suture path with an excessively wide bite nearly sutures the undersurfaces of the dermis together. **C**, Long-term result with scar spread, hypertrophy, and suture marks from excessive tension of the top sutures.

phenomenon creates redundant skin edges that tend to slide over and obscure visibility of the opposite side. At 1 week of follow-up, wounds with this phenomenon will have inversion and uneven wound edges (*Fig 11, C*). There are 2 potential options for troubleshooting. First, the surgeon can remove the initial sutures and replace them with more narrow bites. Second, the surgeon can trim the wound edges where the eversion transitions to inversion (*Fig 12*). In thin skin, this phenomenon is often inevitable, and the latter method of troubleshooting is necessary. Repeat sutures will often result with the same problem.

Goal of deep sutures

The goal of the buried vertical mattress sutures is to transfer tension to the reticular dermis and evert the wound edges to allow for precise and tension-free approximation of the papillary dermis and epidermis.

Quality control checkpoints for placement of deep sutures

1. Is there blood between the wound edges?
 - a. Troubleshooting #1—A gap between the wound edges may result from excessive tension that prevents complete approximation.

Tension may prevent immediate approximation, and the exposed wound edges may bleed.

- b. Troubleshooting #2—A gap between wound edges may result from failure to cinch the buried knot. Eliminate air knots with snug but not strangulating buried sutures.
- c. Troubleshooting #3—An insufficient number of deep sutures will result in weak approximation of the dermis and potential bleeding. Apply the “pull test” to the wound. If lateral traction pulls the wound edges away and reveals a prominent gap, additional buried sutures may be necessary (*Fig 8*).
- d. Troubleshooting #4—A circular path of the buried suture results in bleeding from exposed dermis superficial to the suture loop. A circular suture path is identified by splayed wound edges with minimal to no eversion and by the lack of the dimple often seen with a heart-shaped buried vertical mattress suture (*Fig 9, A*). The circular suture path occurs most commonly as a result of either too narrow a bite of the buried suture or failure to retract the skin edge in an everted position during the throw of the suture. Because of the lack of eversion, the skin edges fail the “snap test.” Troubleshooting requires removal of the initial deep sutures

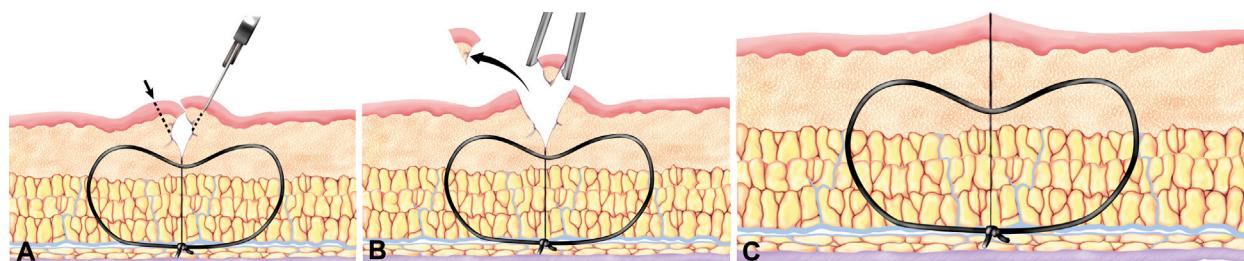


Fig 12. Correction of wound edges with eversion and inversion phenomenon. **A**, Identify the point of collapse where the wound edge begins to invert. **B**, Trim the excess skin beyond the point of collapse. **C**, The newly trimmed wound edges will snap toward the center of the wound to allow tension-free approximation.

and replacement with buried vertical mattress sutures that have a wider bite and wound edges that snap toward each other.

- e. Troubleshooting #5—A buried vertical mattress suture that is placed too widely and deeply can effectively sew the undersides of the dermis together, resulting in exposed dermis that bleeds. The hallmark of this suture path is a prominent dimple far from the wound edge and excessive eversion (Fig 10, A). Because of the bulk of the splayed dermis, the wound edges fail the “snap test.” The correction for this phenomenon is usually replacement of the deep sutures with buried vertical mattress sutures that have a more narrow and superficial bite and wound edges that snap toward each other. However, if the exposed dermis is minimal, it may be possible to trim the splayed dermis and approximate the edges without replacing the buried sutures.
- f. Troubleshooting #6—Failure to throw the buried vertical mattress sutures with mirror images on both sides may result in bleeding of the exposed dermis on the elevated wound edge (Fig 6). The side with the deeper bite (ie, deeper relative to the epidermal edge) will ride higher than the side with the more superficial bite and the exposed dermis will bleed readily. Correction requires replacing the deep suture more accurately, trimming the high side to match the low side, or placing cuticular sutures to align the edges more precisely.

2. Are both wound edges clearly visible?
 - a. Troubleshooting #1—One side of the wound may slide over the opposite side like shingles on a roof when the bites of the deep suture are not mirror images. The side with the more superficial bite (ie, closer to the epidermis)

may slide under the edge of the opposing side. Troubleshooting may include either replacing the deep sutures more accurately or by trimming the high side to match the low side.

- b. Troubleshooting #2—Buried vertical mattress sutures with wide bites in weak dermis may create an upward slope that plateaus or inverts before reaching the wound edge (Fig 10). This eversion—inversion phenomenon creates redundant skin edges that tend to slide over and obscure visibility of the opposite side. There are 2 potential options for troubleshooting. First, the surgeon can remove the initial sutures and replace them with more narrow bites. Second, the surgeon can trim the wound edges where the eversion transitions to inversion (Fig 12).

REPAIRING TISSUE: PLACING SUPERFICIAL SUTURES

Key points

- Superficial sutures correct minor height discrepancies of the wound edges after placement of the buried sutures
- Ideally, cuticular sutures bear minimal to no tension
- Skin with thin dermis requires a higher frequency of sutures (ie, sutures placed closer together) and suture bites that are closer to the wound edge

Even with careful technique with deep sutures, the wound edges frequently benefit from an additional layer of superficial sutures for precise approximation of the epidermal edges. If the deep sutures have been placed effectively, the epidermis and dermis should not have a gap between them and the top sutures should not need to bear tension. However, minor height discrepancies after placement of the deep sutures are common. The

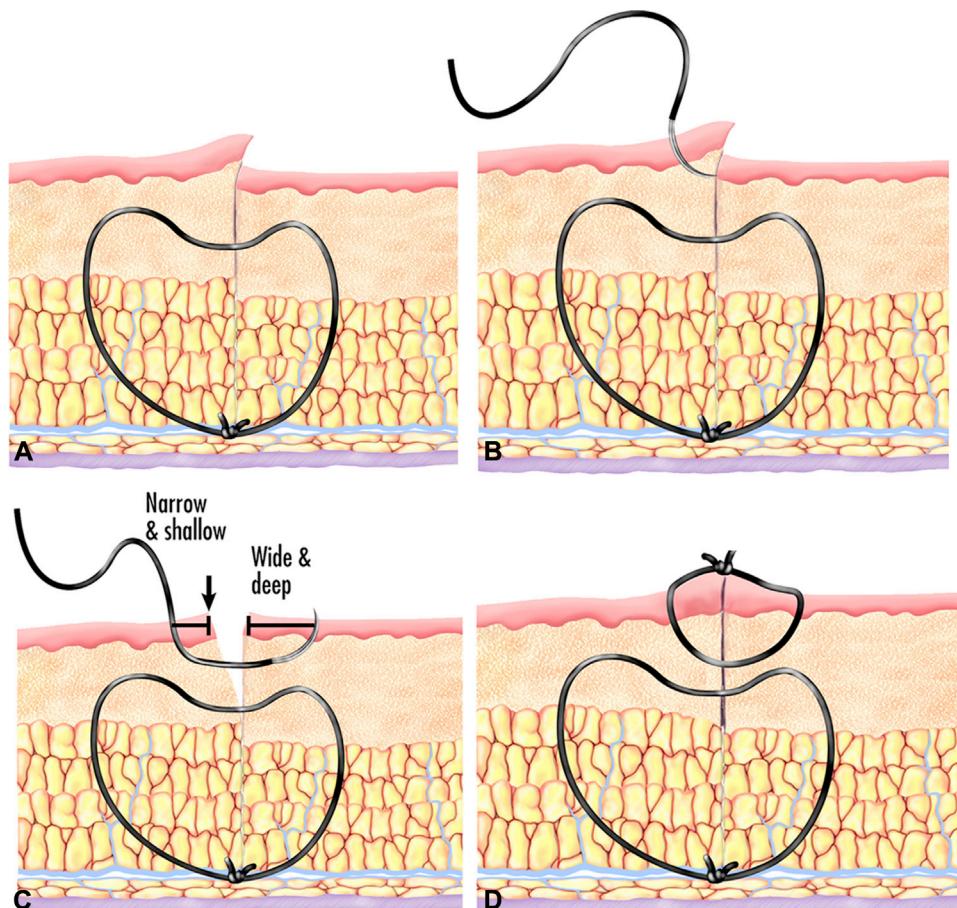


Fig 13. **A**, The buried vertical mattress suture has been placed with unequal bites, resulting in a height discrepancy of the wound edges. **B**, To correct the height discrepancy with top sutures, it is often easiest to bite the high side first with a shallow, narrow throw. **C**, After biting the high side, the wound edge can be depressed to match the lower side, and a deeper, wider bite is thrown on the low side. **D**, The completed top suture corrects the height discrepancy.

primary purpose of the superficial sutures is to correct these height discrepancies. The 2 quality control questions after placement of the deep sutures identify wound edges that will benefit from top sutures. If both wound edges are not clearly visible or if there is bleeding from the exposed dermis, then fine corrections with the top sutures will be necessary.

The type and size of the suture and the size of the needle influence execution of the top sutures. A few general principles apply. First, smaller caliber sutures have a lower risk of leaving track marks compared to thicker caliber sutures. The effective placement of buried vertical mattress sutures nearly eliminates tension on the wound edges and allows the surgeon to use lower caliber sutures. Second, smaller suture needles (eg, P-3) should be used to suture delicate wound edges to avoid tearing. Finally, sutures should be removed as early as possible to avoid track marks. In wounds with

effective placement of deep sutures, the top sutures do not bear tension and can be removed within 5 to 7 days in most cases, especially on the head and neck. Leaving superficial sutures for a longer time offers little advantage, because the deep sutures bear the tension that keeps the wound from dehiscing.^{16,17}

Once the surgeon has chosen the suture materials, the key decisions that the surgeon must make are the spacing between the epidermal sutures and the distance of the suture bites from the wound edge. In general, skin with a thinner dermis requires a higher frequency of sutures (ie, sutures placed closer together) and suture bites that are closer to the wound edge. The ideal distance from the wound edge supports eversion to a peak without collapse. If the bite of the superficial suture is too far from the wound edge, it can create the same eversion–inversion phenomenon as seen with an excessively wide bite with a deep suture.

Table I. Review of checkpoints and methods of error correction

Surgical technique	Quality control checkpoint	Technical error	Correction of errors
Incising	<ol style="list-style-type: none"> 1. Has the incision achieved uniform release to the desired anatomic plane? 2. Do the incised wound edges have a sharp perpendicular edge and no bevel? 3. Are the wound edges cut cleanly without jagged edges? 	<p>Incomplete incision, or skin edges not released Incision extends more deeply than the intended depth of excision and undermining Beveled dermis Beveled subcutaneous fat Jagged wound edges</p>	<p>Complete the incision to the desired depth to get uniform release Ensure that the subsequent steps of excision and undermining occur in the more superficial, correct anatomic plane</p> <ol style="list-style-type: none"> a. Ensure that the angle of the scalpel is perpendicular to the plane of the skin during the incision b. Stabilize the skin during the incision with downward pressure rather than lateral traction c. Consider using a no. 10 scalpel blade for anatomic locations with thick dermis d. Correct the bevel by gripping the redundant tissue with a forceps, apply gentle traction into the wound, and incise through the beveled dermis to create a clean and perpendicular edge <p>Use tissue scissors to trim the fat flush with the vertical face of the incised dermis</p> <ol style="list-style-type: none"> a. Use a sharp scalpel and pass it lightly over the skin, allowing >1 pass to achieve desired depth, if necessary b. Stabilize the skin with gentle downward pressure while incising
Excising	<ol style="list-style-type: none"> 1. Is the excision effortless with minimal bleeding? 2. Does the excision specimen have a uniform thickness without scalloped edges of its base? 3. Does the base of the wound have a uniform depth at the desired anatomic plane? 	<p>Excision is difficult or causes excessive bleeding Excision specimen has uneven thickness The base of the excision specimen has scalloped edges The base of the wound is too shallow The base is deeper than the intended surgical plane</p>	<p>Evaluate the surgical plane and redirect excision to optimal plane as necessary</p> <p>Assess base of wound to identify transitions of surgical planes. Consider using scissors, rather than a scalpel, in order to gain the tactile feedback that helps to maintain a uniform anatomic plane</p> <p>Consider using scissors, rather than a scalpel, in order to gain the tactile feedback that helps to maintain a uniform anatomic plane during the excision</p> <p>Excise the remaining superficial tissue to the desired anatomic plane</p> <p>Be careful that undermining occurs in the more superficial, preferred anatomic plane</p>

Continued

Table I. Cont'd

Surgical technique	Quality control checkpoint	Technical error	Correction of errors
Undermining	<ol style="list-style-type: none"> 1. Does undermining occur effortlessly and with minimal bleeding? 2. Can the incised skin edge be retracted in an everted position? 3. Are the wound edges sharply perpendicular along the full thickness of the skin flap from epidermis to the plane of undermining? 	<p>Undermining is difficult or causes excessive bleeding</p> <p>Undermining is difficult because of poor stabilization of the skin edge</p> <p>The incised wound edge cannot be retracted in an everted position</p> <p>The wound edges are not perpendicular because of beveled dermis or fat</p>	<p>Evaluate the surgical plane and redirect excision to optimal plane as necessary</p> <p>Apply countertraction with the skin hook directly over the point of undermining</p> <p>Undermine effectively to allow easy eversion of the skin edge</p> <p>If the wound edges are not perpendicular after undermining, identify and correct any bevel of the dermis or fat</p>
Placing deep sutures	<ol style="list-style-type: none"> 1. Is there blood between the wound edges? 2. Are both wound edges clearly visible? 	<p>Blood is visible between the wound edges</p> <p>One wound edge overlaps and obscures the other</p>	<ol style="list-style-type: none"> a. Excessive tension may prevent complete wound edge approximation b. Eliminate air knots with cinched but not strangulating buried sutures c. Ensure an adequate number of deep sutures to close all gaps. If a circular path of a buried suture is identified, remove the initial deep sutures and replace with buried vertical mattress sutures that have a wider bite and wound edges that snap toward each other d. If the papillary dermis is splayed from deep sutures with excessively wide bites, replace the deep sutures with buried vertical mattress sutures that have a more narrow and superficial bite. If the exposed dermis is minimal, it may be possible to trim the splayed dermis and approximate the edges without replacing the buried sutures e. If profile of the buried sutures does not have a mirror image and 1 dermal edge rides higher, replace the deep suture more accurately, trim the high side to match the low side, or place cuticular sutures to align the edges more precisely <p>a. One side of the wound overlaps the other if the bites of the deep suture are thrown at different depths. If the difference is marked, replace the buried suture with symmetrical bites. If the difference is minimal, consider trimming the high side to match the lower side</p>

Placing top sutures	1. Is there blood between the wound edges?	2. Are both wound edges clearly visible?	Blood is still present between the wound edges	One wound edge overlaps and obscures the other
	b. Redundant skin edges overlap if the bites of the buried suture are too wide. If the difference is marked, repeat the buried sutures with more narrow bites. If the difference is minimal, consider trimming the overlapping wound edges.	a. Check whether the bites of the suture are asymmetric distances from the wound edge. Place an interrupted suture to realign the wound edges precisely b. Check for pleating of the suture from excessive tension. Relieve the tension until pleating diminishes. Check for insufficient tension and interrupted sutures to close any remaining gaps	a. Check whether the bites of the suture are asymmetric distances from the wound edge. Place an interrupted suture to realign the wound edges precisely	a. Check whether the bites of the suture are asymmetric distances from the wound edge. Place an interrupted suture to realign the wound edges, precisely

The top sutures should be thrown with minimal tension. Excessive tension may cause pleating of the wound edges and increases the risk for wound necrosis and suture marks. As a quality control measure, the surgeon should be able to slide 1 arm of the forceps under the suture loop without difficulty. If the top sutures are thrown with tension, a gap will form at the points of entry and exit. The process of reepithelialization begins immediately,^{16,18} so track marks are likely to occur, even if the top sutures are removed before 1 week postsurgery.

The first step in placing accurate top sutures is to recognize which side of the wound is riding higher than the other. The high side either obscures visibility of the lower wound edge by sliding over it like shingles on a roof or it bleeds because its papillary dermis is exposed. The high side of the wound is usually slightly more delicate and can be more challenging to manipulate. It is often more efficient to correct height discrepancies of the wound edge by biting the high side first. The general guideline to correct height discrepancies with top sutures is: "Bite high on the high side, and bite low on the low side." In other words, the needle should approach the high side with a shallow bite in the papillary dermis (ie, close to parallel to the plane of the epidermis) that is relatively close to the wound edge. After showing the tip of the needle between the wound edges, the surgeon has control of this side of the wound. The surgeon must then depress the wound edge until it matches the height of the opposite side. The needle is then passed with a deeper and wider bite that precisely matches the wound edges (Fig 13). The principles to achieve precise wound approximation apply to various methods of placing superficial sutures.

Goal of superficial sutures

The goal of superficial sutures is to align the papillary dermis and epidermis with precision.

Quality control checkpoints for the placement of cuticular sutures

1. Is there blood between the wound edges?

- a. Troubleshooting #1—When the bites of the superficial sutures have asymmetric distances from the wound edge, the side with the wider bite tends to slide over the opposite side like shingles on a roof, and the opposite edge may not be visible. This exposed dermis on the high side may bleed. Placing an interrupted suture may be necessary to realign the wound edges.

- b. Troubleshooting #2—Excessive tension on the superficial sutures, especially in skin with a thin dermis, can lead to pleating of the wound edges between the loops of suture. Pleating often causes height discrepancies, and the exposed dermis on the high side may bleed. Replacing the cuticular sutures with less tension will correct bleeding from pleating. The sutures should be loose enough to allow the surgeon to slide 1 arm of the forceps under the loop without difficulty.
 - c. Troubleshooting #3—Insufficient tension of the cuticular sutures can lead to small gaps between the wound edges and dermal bleeding. Cutaneous sutures should align the wound edges snugly but without strangulation.
2. Are both wound edges clearly visible?
- a. Troubleshooting—When the bites of the cuticular sutures have asymmetric distances from the wound edge, the side with the wider bite tends to slide over the opposite side like a shingle on a roof, and the opposite edge may not be visible. Placing an interrupted suture may be necessary to realign the wound edges.

CONCLUSION

This continuing medical education series provided quality control questions to assess the technical precision of each step of cutaneous surgery: incising, excising, undermining, placing buried sutures, and placing cuticular sutures. These quality control questions provide a methodology for objective self-evaluation and help to identify common technical errors and potential solutions to obtain reproducibly excellent surgical outcomes (Table I).

REFERENCES

1. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: Part I. Update and review of topical hemostatic agents. *J Am Acad Dermatol*. 2013;69:659.e1-659.e17.
2. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: Part II. Electrosurgery in patients with implantable cardiac devices. *J Am Acad Dermatol*. 2013;69:677.e1-e9.
3. Adams B, Levy R, Rademaker AE, Goldberg LH, Alam M. Frequency of use of suturing and repair techniques preferred by dermatologic surgeons. *Dermatol Surg*. 2006;32:682-689.
4. Zitelli JA, Moy RL. Buried vertical mattress suture. *J Dermatol Surg Oncol*. 1989;15:17-19.
5. Weitzul S, Taylor RS. Suturing techniques and other closure materials. In: Robinson JK, Hanke CW, Siegel DM, Fratila A, editors. *Surgery of the skin: procedural dermatology*. 2nd ed. Philadelphia (PA): Elsevier; 2013. pp. 189-209.
6. Tajirian AL, Goldberg DJ. A review of sutures and other skin closure materials. *J Cosmet Laser Ther*. 2010;12:296-302.
7. Kia KF, Burns MV, Vandergriff T, Weitzul S. Prevention of scar spread on trunk excisions: a rater-blinded randomized controlled trial. *JAMA Dermatol*. 2013;149:687-691.
8. Yang DJ, Venkataraman S, Orengo I. Closure pearls for defects under tension. *Dermatol Surg*. 2010;36:1598-1600.
9. Zeng YJ, Liu YH, Xu CQ, Xu XH, Xu H, Sun GC. Biomechanical properties of skin in vitro for different expansion methods. *Clin Biomech (Bristol, Avon)*. 2004;19:853-857.
10. Wilhelm BJ, Blackwell SJ, Mancoll JS, Phillips LG. Creep vs. stretch: a review of the viscoelastic properties of skin. *Ann Plast Surg*. 1998;41:215-219.
11. LoPiccolo MC, Balle MR, Kouba DJ. Safety precautions in Mohs micrographic surgery for patients with known blood-borne infections: a survey-based study. *Dermatol Surg*. 2012;38(7 Pt 1):1059-1065.
12. Perry AW, McShane RH. Fine tuning of the skin edges in the closure of surgical wounds. Controlling inversion and eversion with the path of the needle—the right stitch at the right time. *J Dermatol Surg Oncol*. 1981;7:471-476.
13. Nevarre DR. Increasing efficiency in the operative field: knot tying, instrument ties, and locking the suture. *Ann Plast Surg*. 1998;40:313-315.
14. Dinsmore RC. Understanding surgical knot security: a proposal to standardize the literature. *J Am Coll Surg*. 1995;180:689-699.
15. Weng R, Li Q, Zheng Y. Reduce suture complications by applying proper knot tying techniques. *Dermatol Surg*. 2010;36:1314-1318.
16. Findlay CW Jr, Howes EL. The effect of edema on the tensile strength of the incised wound. *Surg Gynecol Obstet*. 1950;90:666-671.
17. Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. *Am J Surg*. 1998;176(2A Suppl):26S-38S.
18. Martin P. Wound healing—aiming for perfect skin regeneration. *Science*. 1997;276:75-81.

Teledermatology: From historical perspective to emerging techniques of the modern era

Part I: History, rationale, and current practice

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Learning objectives

After completing this learning activity, participants should be able to discuss the field of telemedicine from a historical perspective, including key challenges faced by practitioners, and how specific technological advances have been used to overcome them; describe the burden of skin disease and maldistribution of specialists faced by patients in the United States and around the world; characterize the teledermatology practice models that are currently available; accurately discuss the status of teledermatology research, including its reliability and accuracy, outcomes data, and patient/provider satisfaction with the technology and identify regions, both domestic and international, in which teledermatology has been successful in providing skin care to underserved populations.

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Telemedicine is the use of telecommunications technology to support health care at a distance. Technological advances have progressively increased the ability of clinicians to care for diverse patient populations in need of skin expertise. Dermatology relies on visual cues that are easily captured by imaging technologies, making it ideally suited for this care model. Moreover, there is a shortage of medical dermatologists in the United States, where skin disorders account for 1 in 8 primary care visits and specialists tend to congregate in urban areas. Even in regions where dermatologic expertise is readily accessible, teledermatology may serve as an alternative that streamlines health care delivery by triaging chief complaints and reducing unnecessary in-person visits. In addition, many patients in the developing world have no access to dermatologic expertise, rendering it possible for teledermatologists to make a significant contribution to patient health outcomes. Teledermatology also affords educational benefits to primary care providers and dermatologists, and enables patients to play a more active role in the health care process by promoting direct communication with dermatologists. (J Am Acad Dermatol 2015;72:563-74.)

Key words: dermatology workforce; Internet; smartphone; store-and-forward; teledermatology; telemedicine.

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Abbreviations used:

AAD:	American Academy of Dermatology
RT:	real-time
S&F:	store-and-forward
TD:	teledermatology

INTRODUCTION

History of telemedicine

Key points

- **Telemedicine is medicine practiced at a distance**
- **Telemedicine's development paralleled urbanization and subspecialization**
- **Telecommunication advances enhanced the practicality of telemedicine**

Telemedicine uses telecommunications technology to convey clinical information from patients to remotely situated providers. Its development occurred in parallel with urbanization and the development of technologies that quickly or instantly link individuals and allow for the rapid conveyance of information across great distances. Telemedicine represents an evolving attempt to meet the needs of diverse patient populations with a variety of dermatologic complaints, although it may afford the greatest benefits to patients that were previously underserved by skin care experts for geographic and/or economic reasons. Indeed, it may have the potential to bring about a “disruptive innovation” that, in part, transforms traditional dermatology practice. There may be a variety of situations where teledermatology (TD) may appropriately substitute for a traditional dermatology encounter with less cost and/or improved efficiency.

Telemedicine can be traced to the early 1900s, when ship captains used radio to receive medical advice.^{1,2} In 1906, Einthoven used telephone lines to transmit electrocardiograms, allowing him to monitor patients from afar.^{3,4} Telemedicine was later used to monitor astronauts' vital signs during the Space Age.⁵ In the late 1950s, National Aeronautics and Space Administration (NASA) technology supported telemedicine for patients living on the Arizonan Papago Indian Reservation and, later, in rural Alaska.⁶

Television provided the first mechanism for live transmission of visual data with high fidelity.³ The first analog units required expensive equipment and technicians, limiting their use to large-scale academic endeavors rather than day to day practice. In the 1950s, televisions linked national medical society meetings.⁷ In 1965, Dr Michael DeBakey showed an aortic valve replacement using NASA's

Early Bird satellite to connect hospitals in Texas and Switzerland.⁷

The development of analog to digital compressors in the 1980s made digital video teleconferencing possible by converting images into electronic binary code.³ Television alone, however, did not provide sufficiently high-quality images compared to still photography. Widespread Internet use provided the missing link by making store-and-forward (S&F) telemedicine possible, allowing providers to instantly relay high-resolution still images and clinical histories to experts around the world.

Mobile technology is now increasing the utility of telemedicine. In many regions, wired connectivity has lagged behind the development of wireless networks. In 2012, the World Bank estimated that 75% of the world's population had access to a mobile phone, up from 60% just 3 years earlier.⁸ Devices are continuously becoming less expensive and more powerful, while transmission networks double their bandwidth every 1.5 years and are continually extended into new territories.⁸ The medical mobile application market is growing rapidly.^{8,9} A recent study reported a total of 229 dermatology-related mobile applications, approximately half of which are intended for patient use.¹⁰ Smartphones represent the possibility of interconnectedness across social, technological, and medical dimensions.

The burden of skin disease

Key points

- **The burden of skin disease is vast in both developed and developing countries**
- **The demand for medical dermatologists exceeds the current supply**
- **Teledermatology may partially solve health-care disparities**

TD, defined as the practice of providing skin care at a distance using telecommunications technologies, has been used by the US Department of Defense for several decades,³ and began to be described in the medical literature in the early 1990s.¹¹⁻¹⁴ Its use was reported in the literature in 1993 based on experiences in Norway, where telemedicine gained substantial ground during this time in a variety of medical specialties with highly visual components, including radiology and pathology.¹¹⁻¹³ In the United States, TD was described as early as 1995 as a mechanism for providing care to underserved populations in rural Oregon.¹⁴ Figure 1 shows the growing body of TD literature over the last 20 years.

TD has the potential to greatly impact dermatology. The prevalence of skin diseases collectively

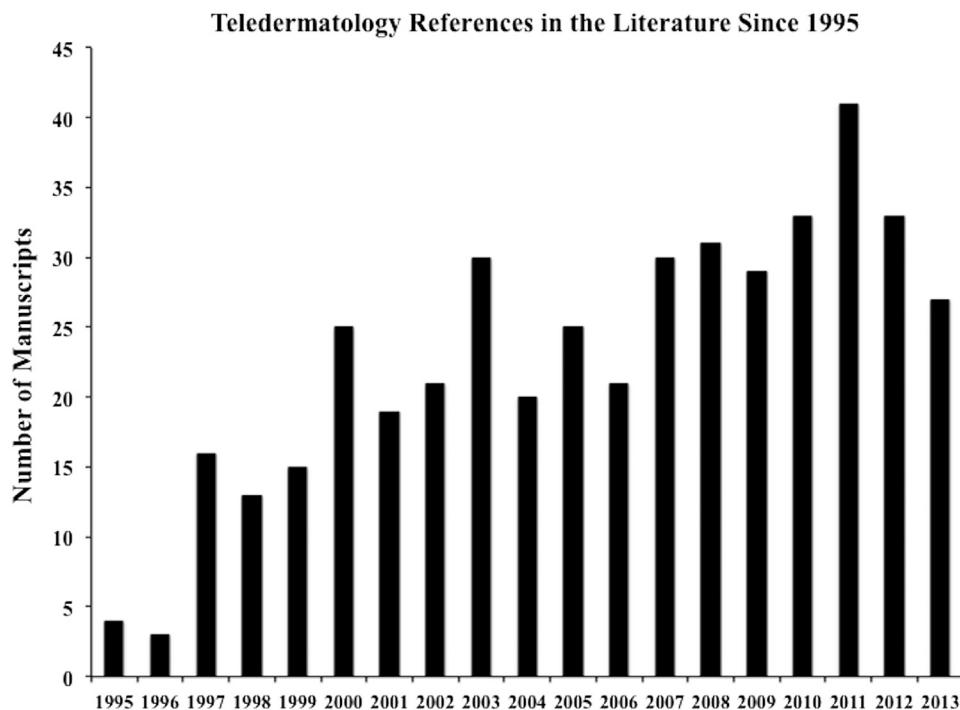


Fig 1. Teledermatology literature since 1995. The term “teledermatology” first appeared in the medical literature in the early 1990s.¹¹⁻¹⁴ A literature search in Medline through the end of 2013 for articles mentioning “teledermatology” found a steadily growing number of articles related to this topic.

exceeds that of obesity, hypertension, and cancer.¹⁵ Skin disease accounts for 12.4% of primary care visits in the United States, and most patients with dermatologic complaints contact only their family physician.¹⁶ However, an Irish study of nearly 500 cases found that dermatologists are significantly more successful than family physicians (87% vs 22%) at diagnosing biopsy-proven skin cancers.¹⁷ Another study involving 656 consecutive general practitioner referrals to an Australian dermatology clinic, 151 of which had histologic confirmation, found that general practitioners agreed with biopsy-proven diagnoses in 24% of cases, whereas dermatologists agreed in 77% of cases.¹⁸ Additional investigations have found that dermatologists are superior to primary care providers at correctly diagnosing melanomas and managing pigmented lesions.¹⁹

While the number of dermatologists has grown more quickly than the US population—increasing from 1.9 to 3.2 per 100,000 persons between 1970 and 2010, respectively^{20,21}—evidence suggests a shortage of medical dermatologists.^{20,22-24} The average wait time for an appointment was 33.9 days in 2009²⁵; a 2006 study revealed that even for urgent conditions (ie, changing nevi), patients experienced long wait times.²³ Interestingly, waits are reportedly 50% shorter for cosmetic procedures.²⁶ A recent study revealed that a pediatric

dermatologist shortage disproportionately affects Medicaid-insured children.²⁷ This suggests that payment structures and other socioeconomic factors may be contributing to disparities in skin care delivery.

One factor that may be contributing to long wait times and the apparent shortage of skin expertise is the geographic distribution of dermatologists (Fig 2). In the 3 US urban areas with the highest density of dermatologists (Boston, MA; Palo Alto, CA; and New York City, NY), there are 25 dermatologists per 100,000 people, compared to 0.17 per 100,000 in the 3 lowest-density cities.²¹ Moreover, hundreds of rural counties, particularly in the central and western regions of the United States, have no local dermatologists to serve their respective patient populations on an in-person basis. Economic factors may also play a role; many dermatologists decline to accept some types of health insurance (eg, Medicaid), contributing to the difficulty some patients have in obtaining an appointment with a dermatologist. Although the relationship between geographic and economic disparities in dermatology service delivery is not clear, both factors may be at play in many regions, such that health care disparities are compounded for millions of patients.

Finally, there is a trend among dermatologists toward early retirement and shorter workweeks,^{20,22}

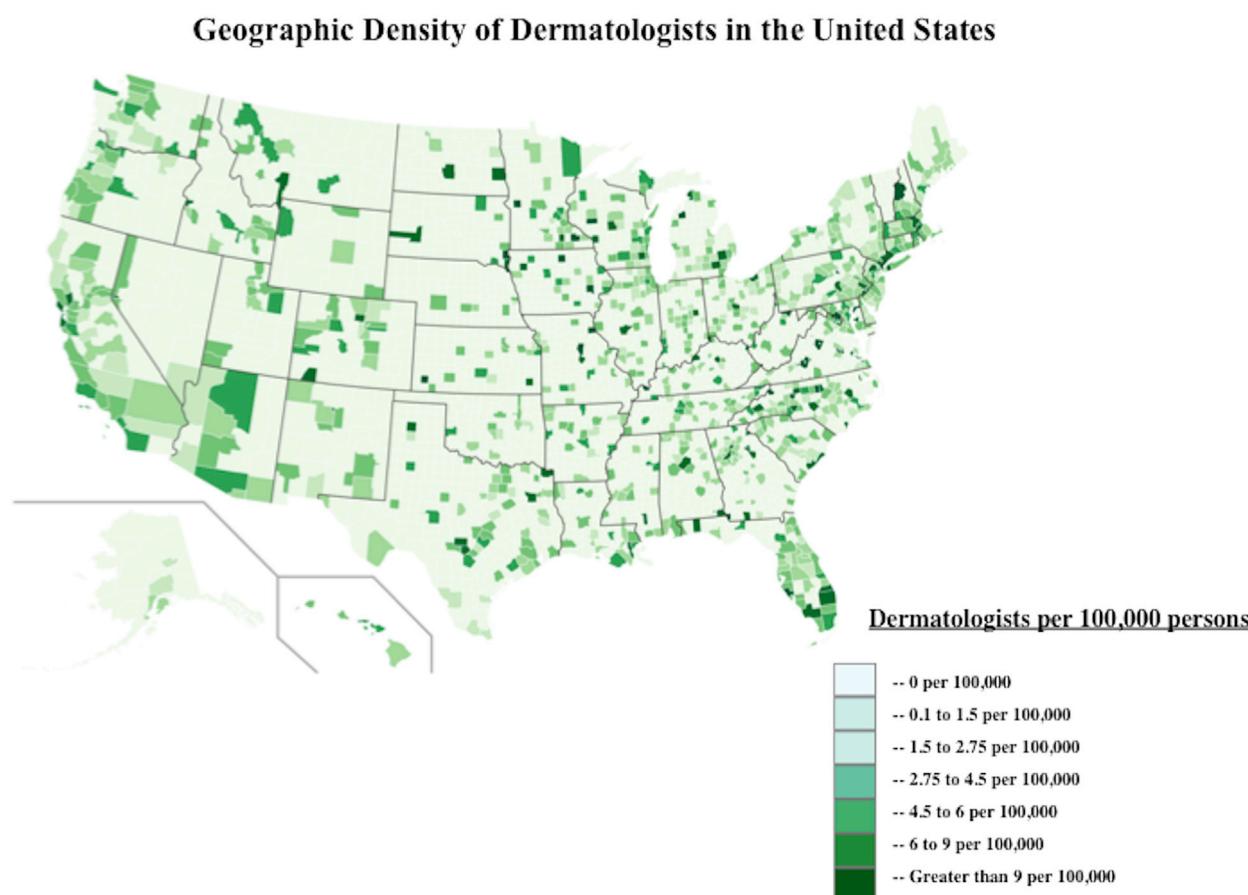


Fig 2. Geographic distribution of practicing dermatologists within the United States. Since 1970, the geographic density of dermatologists has increased from 1.9 to 3.2 per 100,000 persons.²¹ However, there is a nationwide shortage of medical dermatologists. (Courtesy of the American Academy of Dermatology: dermatology workforce resources and distribution map. Accessed September 1, 2013.¹²⁸ Modified version of blank map created by user Theshibboleth [http://commons.wikimedia.org/wiki/File:Blank_US_Map.svg]. Permission is granted to copy, distribute, and/or modify this document under the terms of the GNU Free Documentation License, version 1.2 or any later version published by the Free Software Foundation; with no invariant sections, no front-cover texts, and no back-cover texts.)

perhaps exacerbating the shortage of dermatology services. The economic recession at the end of the last decade had a smaller impact on demand for dermatologists' services than was seen in other medical fields, probably reflecting the discrepancy between the supply of and demand for dermatologic expertise, and suggesting important implications for improving or enhancing current mechanisms of accessing it.²⁸ TD may mitigate inequities in health care delivery and recruit part-time or retired dermatologists.²⁹

Teledermatology technologies and practice models

Key points

- The 3 technological modalities of teledermatology are store-and-forward, real-time, and hybrid

- **Store-and-forward is the most widely used modality**
- **Practice models include consultative, triage, direct care, and follow-up**

Three distinct TD modalities have been developed to bring care to remote populations.³⁰ Modality selection may reflect referring providers' capabilities, teleconsultants' practice structures, and other aspects of local health care system infrastructures, including choices made by payers, hospitals, and individual physicians. Table I shows the advantages and disadvantages of each modality. In S&F TD, consultants access data asynchronously, interfering less with daily workflow. Real-time TD (RTTD) enables direct interaction via a live video connection, requiring coordination between

Table I. Advantages and disadvantages of existing teledermatology technologies*

	Store-and-forward	Real-time	Hybrid
Advantages	More efficient for physicians practicing across time zones	May save time by clarifying consultant's questions Greater opportunity for patient education	Combines time-saving aspects of RT with quality of digital still images May improve patient satisfaction compared to S&F alone
Disadvantages	May require repeat consultation if clinical histories are incomplete Less opportunity for patient education	Requires significant bandwidth Less convenient for practice across time zones Video images have lower quality/resolution than still images	Requires significant bandwidth Less convenient for physicians practicing across time zones

S&F, Store-and-forward; RT, real-time.

*The three technological modalities of teledermatology are store-and-forward, real-time, and hybrid. The selection of a teledermatology modality depends upon a variety of factors, including patient and provider convenience, equipment cost, and access to high-speed Internet service.

providers but potentially saving time by immediately clarifying aspects of complaints. Hybrid models merge advantageous aspects of both S&F and RTTD.

Four TD practice models have been identified: consultative, triage, direct care, and follow-up.³¹ The most commonly used is the consultative model, in which teledermatologists make recommendations from afar using any of the aforementioned technological modalities and referring providers assume the responsibility for adopting recommendations. The triage model uses TD to prioritize patient care and determine the need for in-person visits. This may improve access by reducing unnecessary referrals or shortening wait lists, the implications of which may be particularly important in underserved and/or resource-poor settings, although TD may be generally useful and efficient for appropriate triage. The direct care model supports direct communication between dermatologists and patients with skin complaints. More specifically, patients using this model photograph their own skin lesions and send images directly to consultants. This approach is limited by willingness to prescribe medications to patients not seen in a clinic setting, but it affords the greatest flexibility to many patients. The follow-up model enables remote monitoring of chronic skin conditions, such as psoriasis or stasis ulcers, that would otherwise warrant frequent clinic visits to assess disease activity and optimize therapy. While the follow-up model (which is a form of direct care) may be used with either direct or indirect communication lines between patients and dermatologists, it is typically described in settings of established in-person care, for which subsequent remote

follow-up sessions may save both time and money for patients with chronic conditions.³¹

EVIDENCE SUPPORTING THE USE OF TELEDERMATOLOGY

Usefulness and reliability

Key points

- Diagnostic and management decisions made via teledermatology are reliable and accurate
- Clinical outcomes are reportedly similar to those of standard care

Multiple studies support the reliability (ie, agreement) and accuracy of TD.³²⁻³⁹ Complete agreement means consultants arrive at the same single diagnosis, whereas partial agreement means they list several diagnoses, some of which match one another. A systematic review found that S&F TD typically yields high degrees of complete interobserver agreement and even greater degrees of partial agreement.⁴⁰ The same relationship has been reported for diagnostic concordance among teledermatologists using RTTD models.⁴⁰ Hybrid modalities are reportedly no more reliable than S&F alone.⁴¹ The diagnostic accuracy of S&F TD, based on histopathology, has been reported to be high in multiple studies.^{40,42-44} Management decisions made at a distance using either modality have also been highly concordant.⁴⁰ Despite the success of telemedicine, the accuracy of in-person dermatology is reportedly 11% greater than TD.³⁶

In-person care and S&F TD yield similar outcomes, including improvement in clinical symptoms and time to intervention in patients with skin cancer.^{32,37,45-47} S&F TD obviated the need for an in-person consultation in 13% to 71% of cases of

various skin disorders,^{40,42,48-53} with a 51% rate in the largest study.⁵⁴ RTTD and hybrid modalities have been even more successful at this.^{42,55-58}

Participant satisfaction

Key points

- Patients and providers report high satisfaction with teledermatology
- Patients are typically willing to pay for teledermatology consults

Patient satisfaction with TD is reportedly comparable to in-person care,^{48,59-66} in part because TD reduces wait times.^{32,54,61,67-71} Physicians engaging in RTTD reportedly communicate with a style and content similar to standard care, supporting the ability to establish rapport via TD.⁷⁰ A randomized trial found no significant difference in patient quality of life for S&F TD compared to conventional care after 3 and 9 months.⁷² Patient satisfaction may also be inferred from their willingness to pay for TD consults.^{73,74}

Rural patients and physicians rate their experiences higher than urban counterparts, suggesting that satisfaction reflects the regional availability of care.⁶⁰ Referring physicians rate their experience favorably and perceive that TD affords educational as well as clinical benefits.^{42,60,75,76} Dissatisfying aspects of TD cited by some patients have included concerns about improper treatment and insufficient follow-up.⁶²

Patient-centered teledermatology

Key points

- Patient-centered teledermatology, in which patients generate and send images of their skin lesions, enables rapid communication with health care providers
- Patients are reportedly satisfied with this convenient modality and take images of sufficient quality for telediagnosis

The direct care, or patient-centered, model of TD affords a reliable and convenient platform for patients who wish to consult or follow-up with dermatologists remotely.^{77,78} Patients typically generate images of sufficient quality for diagnosing or monitoring their skin conditions, although image quality may be inferior to staff-generated images.^{74,79-83} In studies of patients with acne and psoriasis, patient-centered follow-up yielded similar clinical outcomes while saving patients both time and money.^{46,77,78}

Patient-centered modalities generally have high favorability that improves as patients gain

experience.^{74,84} In 1 study, 63% were comfortable with teleconsultation before their experience, compared to 75% afterward.⁷⁴ Smartphones have been used successfully to closely monitor for negative effects of biologic therapies in patients with psoriasis.⁸³ Investigators studying the direct care model in patients with psoriasis reported good clinical outcomes and positive impacts on self-care behavior, dermatologic quality of life, medication compliance, and the patient–physician relationship.⁸⁵

Advanced noninvasive imaging modalities, such as MelaFind, may enhance the objectivity of remote evaluation by assisting in skin biopsy decisions regarding atypical pigmented lesions.⁸⁶ While these tools were not originally intended for use by patients, in the future they may be helpful in this setting to physicians caring remotely for high-risk populations that require regular follow-up. In the meantime, a variety of smartphone applications have been developed for patient use that make reliability claims regarding the ability to render accurate melanoma diagnoses.¹⁰ These technologies will be discussed further in part II of this continuing medical education review.

TELEDERMATOLOGY TODAY

Global uses of teledermatology

In 2010, 38% of countries had some form of TD program, and 30% had government agencies devoted to TD.⁸⁷ High-income countries have more initiatives than low-income countries.⁸⁷ TD has thrived in highly integrated systems, such as Kaiser Permanente in California and in countries with state-supported universal health care.^{88,89}

TD is an answer to long waiting lists in an era of heightened demand for specialists, and has gained value as a mechanism for triaging patients in both the outpatient and inpatient settings.^{45,75,76,90,91} At least 32% of Dutch general practitioners participate in TD with dermatologists to whom they would normally refer patients, such that TD reduces the typical volume of in-person visits.⁷⁶ TD is also being used in the hospital setting, a use that may help to mitigate the effects of an inpatient medical dermatologist shortage.⁹¹

Oncology nurses use TD to monitor for dermatologic toxicities of chemotherapies.^{92,93} TD is effective in treating both pediatric and adult populations, which may partially mitigate the shortage of pediatric dermatologists.⁹⁴⁻⁹⁶ TD is also used to manage chronic conditions, such as psoriasis and stasis ulcers.^{52,97-100}

Locations of Active Teledermatology Programs in the United States

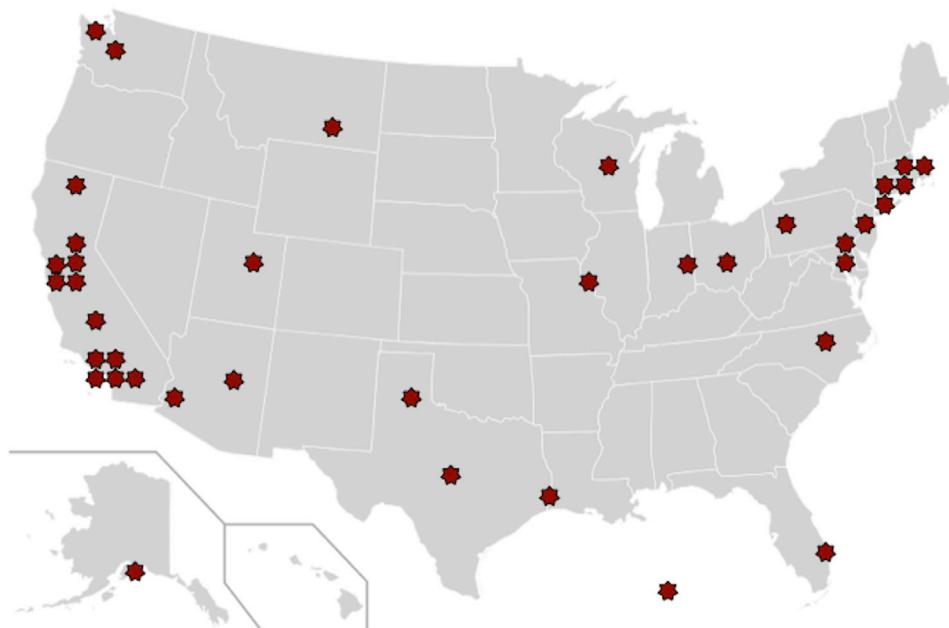


Fig 3. Locations of active teledermatology programs in the United States (2012). Please note that the star positioned in the Gulf of Mexico represents an active teledermatology program at the Veterans Affairs hospital in San Juan, Puerto Rico. (Courtesy of the American Telemedicine Association.¹⁰⁵ Modified version of blank US county map; Wikiprojects; original author unknown [http://en.wikipedia.org/wiki/File:Map_of_USA_with_county_outlines.png]. Permission is granted to copy, distribute, and/or modify this document under the terms of the GNU Free Documentation License, version 1.2 or any later version published by the Free Software Foundation; with no invariant sections, no front-cover texts, and no back-cover texts.)

Teledermatology in the United States

Key points

- Teledermatology has been used successfully by the US military
- The volume of commercial teleconsultations has steadily grown
- Teledermatology is used to care for geographically or economically disadvantaged populations

The US military has used TD for 2 decades.^{101,102} Military teledermatologists at 40 sites nationally have facilitated nearly 40,000 TD encounters as of 2012.^{89,103,104} By caring for deployed soldiers, the network has saved approximately \$30.4 million in travel costs since 2004.¹⁰³

Teledermatologists elsewhere in the United States practice in private and academic settings. Although the number of active US TD programs (Fig 3) dropped from 62 to 38 from 2003 to 2012, total consultation volume increased nearly 2-fold.^{89,105} Eighty-one percent of programs use S&F and 19% use hybrid models.⁸⁹ Integrated health care delivery systems account for the largest

teleconsultation volume, followed by government-funded programs.⁸⁹

TD has gained support as a mechanism for serving patients that were previously underserved by dermatologists for geographic or economic reasons.¹⁰⁶ In 2011, 75% of Californian TD patients had incomes below 200% of the federal poverty level, and they tended to live in rural areas.^{89,107} The American Academy of Dermatology (AAD) sponsors AccessDerm, a volunteer service that facilitated 962 consultations between 2007 and early 2014.¹⁰⁸ One obstacle is that members can only answer cases from states in which they are licensed, and only 16 states had registered clinics in early 2014.¹⁰⁸

Teledermatology in developing nations

Key points

- Patients in developing nations experience a disproportionate burden of skin disease
- Most international programs use the store-and-forward modality of teledermatology
- Mobile teledermatology will expand access to dermatologists

Many patients in the developing world never see a dermatologist, despite a disproportionate burden of skin disease. In sub-Saharan Africa, skin complaints account for up to 24% of physician visits,^{109,110} while only 14% of sub-Saharan African countries have trained dermatologists or dermatopathologists.¹¹¹ The HIV/AIDS epidemic brought about a rise in the prevalence of and stigma associated with skin disease.¹¹² Morbidity is significant, affecting patients through stigmatization, disfigurement, disability, and/or refractory symptoms, such as itching.¹¹³ Patients are typically treated by ancillary staff with limited dermatology knowledge.¹¹⁴

Efforts to alleviate the worldwide maldistribution of dermatologists largely use S&F TD because of the lower costs and greater feasibility for clinicians practicing across time zones.^{90,112} The use of stationary S&F TD at a site in South Africa reduced the burden of skin disease and enhanced the diagnostic acumen of general practitioners.^{112,115} Another international TD endeavor is the Africa Teledermatology Project.¹¹⁶ Since 2007, participating physicians use S&F TD to transfer information from underserved sites in Africa to dermatologists in the United States, Europe, and Australia.¹¹⁷ Apart from clinical services, the project educates rural health care workers through Web-based learning that uses local cases as examples.¹¹⁷

International TD programs face special challenges, including patient illiteracy, lower follow-up rates, resistance to foreign involvement, and the unavailability or unaffordability of teleconsultants' diagnostic or therapeutic recommendations.^{90,118} The cooperation of regional governments and health care providers is necessary to build sustainable initiatives.⁹⁰ Another challenge is that, even when eager to cooperate, nondermatologist health care providers may initially lack the skills needed to take thorough dermatologic histories and capture high-quality images.¹¹⁹ Insufficient clinical information may exacerbate the tendency of teledermatologists to request additional diagnostic testing compared to face to face dermatologist counterparts, as suggested by the results of a recent study involving HIV-positive patients in Botswana.¹¹⁹ These management plan discrepancies are particularly problematic because access to dermatopathology interpretation is tenuous in the developing world; in nearly one-third of sub-Saharan African countries, it takes >1 month to receive a tissue diagnosis.^{111,119} Another challenge has traditionally been limited Internet access, which has become less problematic because of increased adoption of smartphone technology.

Teledermatology as an educational tool

Key points

- **Teledermatology has both clinical and educational benefits**
- **Smartphones enable Web-based learning in remote settings**
- **Teledermatology may enhance dermatology resident training**

TD facilitates learning by exposing physicians to cases they would not otherwise see, connecting images with case histories, and providing a forum for academic discussion. TD has been used successfully to supervise remote training of general practitioners in the United Kingdom where, in 1 study, 63% of teleconsultations were felt to be of educational value.⁶³ The Army Knowledge Online initiative supports deployed health care personnel via a rapid-response TD service.¹⁰⁴ Program usage has declined as primary providers become more knowledgeable about dermatology through the TD process.¹⁰⁴ Videoconferencing has been used to educate internal medicine residents in underserved areas.¹²⁰ In 2009, physicians in the Pacific Northwest implemented S&F TD to serve local veterans. They simultaneously developed a curriculum to remotely train physicians.¹²¹ Investigators reported improved dermatology knowledge and successful acquisition of basic surgical skills.¹²¹ In Botswana, smartphones loaded with mobile health applications enable the rapid transfer of information for both consultation and resident education.¹²²

TD also connects dermatologists to one another for the purposes of continuing medical education and super-specialized referral.^{123,124} TD has been used to supervise dermatology resident training at urgent care facilities in New York and at Brooke Army Medical Center in San Antonio, Texas.^{104,125} In 2008, the AAD began sponsoring US dermatology residents to staff dermatology clinics in Gabarone, Botswana.¹²⁶ The site uses S&F TD and is capable of real-time teledermatopathology, a practice by which dermatopathologists remotely operate microscopes in order to assess biopsy specimens acquired at sites of patient care. The apparatus that has been constructed in Botswana represents the amalgamation of various TD modalities into a single working entity.¹²⁶ TD may also be used as a source of second opinions that connects centers of different sizes and levels of expertise.¹²⁷

CONCLUSION

As summarized above, technological advances have the potential to revolutionize patient care by delivering skin expertise to a broader array of patient

populations than was previously possible and replacing some of the traditional in-person dermatology patient encounters with a more financially and time-efficient mechanism in a variety of economic and cultural settings. A substantial and growing body of literature supports the reliability of TD as a tool for providing care on a remote basis to diverse patient populations with various skin complaints. Remaining challenges include addressing the shortcomings of burgeoning remote diagnostic and/or therapeutic technologies, successfully syncing imaging devices with electronic medical records systems, and confronting concerns regarding the ability of TD to serve patients while maintaining existing legal and ethical practice standards.

In part II of this continuing medical education article, we discuss ways in which novel technologies are currently being used as TD tools. We also address the ways in which these technologies present our specialty with an array of clinical, legal, and ethical challenges that are actively being considered at all levels of government, and which must be addressed as teledermatologists work to build a global network of practicing physicians.

REFERENCES

1. Wootton R. Recent advances: telemedicine. *BMJ*. 2001;323:557-560.
2. Norwegian Centre for Maritime Medicine Web site. History. Available at: <http://www.ncmm.no/about-radio-medico-norway/history>. Accessed September 14, 2014.
3. Vidmar DA. The history of teledermatology in the department of defense. *Dermatol Clin*. 1999;17:113-124.
4. Wurm EM, Hofmann-Wellenhof R, Wurm R, Soyer HP. Telemedicine and teledermatology: past, present and future. *J Dtsch Dermatol Ges*. 2008;6:106-112.
5. Kanthraj G. Newer insights in teledermatology practice. *Indian J Dermatol Venereol Leprol*. 2011;77:276-287.
6. Senel E. History of teledermatology: a technique of the future in dermatology. *Skinmed*. 2010;8:167-170.
7. Debackey ME. Telemedicine has now come of age. *Telemed J E Health*. 1995;1:3-5.
8. The World Bank Web site. Mobile phone access reaches three quarters of planet's population. Available at: <http://www.worldbank.org/en/news/press-release/2012/07/17/mobile-phone-access-reaches-three-quarters-planets-population>. Accessed July 18, 2013.
9. Danzis BSD, Pruitt C. Rethinking the FDA's regulation of mobile medical apps. *The SciTech Lawyer*. 2013;9:26-30.
10. Brewer AC, Endly DC, Henley J, et al. Mobile applications in dermatology. *JAMA Dermatol*. 2013;149:1300-1304.
11. Vorland L. Good experiences with telemedicine in the regional hospital of Tromsø. *Nord Med*. 1992;107:241-243.
12. Rinde E, Nordrum I, Nymo B. Telemedicine in rural Norway. *World Health Forum*. 1993;14:71-77.
13. Holland U, Steinar P. Quality requirements for telemedical services. In: Nymo BJ, ed. *Telemedicine*. Norway: Teklekronikk; 1993. pp. 3-170.
14. Perednia DA. Teledermatology: one application of telemedicine. *Bull Med Libr Assoc*. 1995;83:42-47.
15. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490-500.
16. Verhoeven EW, Kraaimaat FW, Van Weel C, et al. Skin diseases in family medicine: prevalence and health care use. *Ann Fam Med*. 2008;6:349-354.
17. Morrison A, O'Loughlin S, Powell FC. Suspected skin malignancy: a comparison of diagnoses of family practitioners and dermatologists in 493 patients. *Int J Dermatol*. 2001;40:104-107.
18. Tran H, Chen K, Lim AC, Jabbour J, Shumack S. Assessing diagnostic skill in dermatology: A comparison between general practitioners and dermatologists. *Australas J Dermatol*. 2005;46:230-234.
19. Chen SC, Pennie ML, Kolm P, et al. Diagnosing and managing cutaneous pigmented lesions: primary care physicians versus dermatologists. *J Gen Intern Med*. 2006;21:678-682.
20. Resneck J, Kimball AB. The dermatology workforce shortage. *J Am Acad Dermatol*. 2004;50:50-54.
21. Yoo J, Rigel D. Trends in dermatology: geographic density of US dermatologists. *Arch Dermatol*. 2010;146:2013.
22. Kimball AB, Resneck JS. The US dermatology workforce: a specialty remains in shortage. *J Am Acad Dermatol*. 2008;59:741-745.
23. Tsang MW, Resneck JS. Even patients with changing moles face long dermatology appointment wait-times: a study of simulated patient calls to dermatologists. *J Am Acad Dermatol*. 2006;55:54-58.
24. Uhlenhake E, Brodell R, Mostow E. The dermatology work force: a focus on urban versus rural wait times. *J Am Acad Dermatol*. 2009;61:17-22.
25. American Academy of Dermatology web site. Dermatology practice profile survey. Available at: <http://www.aad.org/members/practice-management-resources/dermatology-practice-profile>. Accessed September 1, 2014.
26. Resneck JS, Lipton S, Pletcher MJ. Short wait times for patients seeking cosmetic botulinum toxin appointments with dermatologists. *J Am Acad Dermatol*. 2007;57:985-989.
27. Chaudhry SB, Armbrecht ES, Shin Y, et al. Pediatric access to dermatologists: Medicaid vs. private insurance. *J Am Acad Dermatol*. 2013;68:738-748.
28. Cheng CE, Kimball AB. The canary seems fine: the effects of the economy on job-seeking experiences of recent dermatology training program graduates. *J Am Acad Dermatol*. 2010;63:e23-e28.
29. Levin YS, Warshaw EM. Teledermatology: a review of reliability and accuracy of diagnosis and management. *Dermatol Clin*. 2009;27:163-176.
30. Johnson MN, Armstrong AW. Technologies in dermatology: teledermatology review. *G Ital Dermatol Venereol*. 2011;146:143-153.
31. Pathipati AS, Lee L, Armstrong AW. Health-care delivery methods in teledermatology: consultative, triage and direct-care models. *J Telemed Telecare*. 2011;17:214-216.
32. Hsiao JL, Oh DH. The impact of store-and-forward teledermatology on skin cancer diagnosis and treatment. *J Am Acad Dermatol*. 2008;59:260-267.
33. Edison KE, Ward DS, Dyer JA, Lane W, Chance L, Hicks LL. Diagnosis, diagnostic confidence, and management concordance in live-interactive and store-and-forward

- teledermatology compared to in-person examination. *Teamed J E Health.* 2008;14:889-895.
34. Lim AC, Egerton IB, See A, Shumack SP. Accuracy and reliability of store-and-forward teledermatology: preliminary results from the St George Teledermatology Project. *Australas J Dermatol.* 2001;42:247-251.
 35. Pak H, Welch M, Poropatich R. Web-based teledermatology consult system: preliminary results from the first 100 cases. *Stud Health Technol Inform.* 1999;64:179-184.
 36. Warshaw EM, Hillman YJ, Greer NL, et al. Teledermatology for diagnosis and management of skin conditions: a systematic review. *J Am Acad Dermatol.* 2011;64:759-772.
 37. Lamel S, Chambers CJ, Ratnarathorn M, Armstrong AW. Impact of live interactive teledermatology on diagnosis, disease management, and clinical outcomes. *Arch Dermatol.* 2012;148:61-65.
 38. Gilmour E, Campbell S, Loane MA, et al. Comparison of teleconsultations and face-to-face consultations: preliminary results of a United Kingdom multicentre teledermatology study. *Br J Dermatol.* 1998;139:81-87.
 39. Kvedar JC, Edwards RA, Menn ER, et al. The substitution of digital images for dermatologic physical examination. *Arch Dermatol.* 1997;133:161-166.
 40. American Telemedicine Association web site. Summary of the status of teledermatology research. Available at: <http://www.americantelemed.org/docs/special-interest-group-docs/2011-summary-of-the-status-of-teledermatology-research.pdf?sfvrsn=2>. Accessed September 1, 2014.
 41. Romero G, Sánchez P, García M, Cortina P, Vera E, Garrido JA. Randomized controlled trial comparing store-and-forward teledermatology alone and in combination with web-camera videoconferencing. *Clin Exp Dermatol.* 2010;35:311-317.
 42. Whited JD. Teledermatology research review. *Int J Dermatol.* 2006;45:220-229.
 43. Warshaw EM, Gravely AA, Bohjanen KA, Chen K. Interobserver accuracy of store and forward teledermatology for skin neoplasms. *J Am Acad Dermatol.* 2010;62:513-516.
 44. Massone C, Maak D, Hofmann-Wellenhof R, Soyer HP, Frühauf J. Teledermatology for skin cancer prevention: an experience on 690 Austrian patients. *J Eur Acad Dermatol Venereol.* 2014;28:9-11.
 45. Pak H, Triplett C, Lindquist J, Grambow S, Whited J. Store-and-forward teledermatology results in similar clinical outcomes to conventional clinic-based care. *J Telemed Telecare.* 2007;13:26-30.
 46. Watson AJ, Bergman H, Williams CM, Kvedar JC. A randomized trial to evaluate the efficacy of online follow-up visits in the management of acne. *Arch Dermatol.* 2010;146:406-411.
 47. Kahn E, Sossong S, Goh A, Carpenter D, Goldstein S. Evaluation of skin cancer in Northern California Kaiser Permanente's store-and-forward teledermatology referral program. *Teamed J E Health.* 2013;19:780-785.
 48. Eminović N, de Keizer NF, Wyatt JC, et al. Teledermatologic consultation and reduction in referrals to dermatologists. *Arch Dermatol.* 2009;145:558-564.
 49. Eminović N, Dijkgraaf MG, Berghout RM, Prins AH, Bindels PJ, de Keizer NF. A cost minimisation analysis in teledermatology: model-based approach. *BMC Health Serv Res.* 2010;10:251.
 50. Whited JD, Hall RP, Foy ME, et al. Teledermatology's impact on time to intervention among referrals to a dermatology consult service. *Teamed J E Health.* 2002;8:313-321.
 51. Knol A, van den Akker T, Damstra R, de Haan J. Teledermatology reduces the number of patient referrals to a dermatologist. *J Telemed Telecare.* 2006;12:75-78.
 52. Hofmann-Wellenhof R, Salmhofer W, Binder B, Okcu A, Kerl H, Soyer HP. Feasibility and acceptance of telemedicine for wound care in patients with chronic leg ulcers. *J Telemed Telecare.* 2006;12:15-17.
 53. Moreno-Ramirez D, Ferrandiz L, Ruiz-de-Casas A, et al. Economic evaluation of a store-and-forward teledermatology system for skin cancer patients. *J Telemed Telecare.* 2009;15:40-45.
 54. Moreno-Ramirez D, Ferrandiz L, Nieto-Garcia A, et al. Store-and-forward teledermatology in skin cancer triage: experience and evaluation of 2009 teleconsultations. *Arch Dermatol.* 2007;143:479-484.
 55. Dekio I, Hanada E, Chinuki Y, et al. Usefulness and economic evaluation of ADSL-based live interactive teledermatology in areas with shortage of dermatologists. *Int J Dermatol.* 2010;49:1272-1275.
 56. Woottton R, Bahaddinbeigy K, Hailey D. Estimating travel reduction associated with the use of telemedicine by patients and healthcare professionals: proposal for quantitative synthesis in a systematic review. *BMC Health Serv Res.* 2011;11:185.
 57. Loane M, Bloomer S, Corbett R, et al. A comparison of real-time and store-and-forward teledermatology: a cost-benefit study. *Br J Dermatol.* 2000;143:1241-1247.
 58. Edison KE, Chance L, Martin K, Braudis K, Whited JD. Users and nonusers of university-based dermatology services following a teledermatology encounter: a retrospective descriptive analysis. *Teamed J E Health.* 2010;17:14-18.
 59. Collins K, Walters S, Bowns I. Patient satisfaction with teledermatology: quantitative and qualitative results from a randomized controlled trial. *J Telemed Telecare.* 2004;10:29-33.
 60. Klaz I, Wohl Y, Nathansohn N, Yerushalmi N, Sharvit S. Teledermatology: quality assessment by user satisfaction and clinical efficiency. *Isr Med Assoc J.* 2005;7:487-490.
 61. Whited JD, Hall RP, Foy ME, et al. Patient and clinician satisfaction with a store-and-forward teledermatology consult system. *Teamed J E Health.* 2004;10:422-431.
 62. Hsueh MT, Eastman K, McFarland LV, Raugi GJ, Reiber GE. Teledermatology patient satisfaction in the Pacific Northwest. *Teamed J E Health.* 2012;18:377-381.
 63. Thind CK, Brooker I, Ormerod AD. Teledermatology: a tool for remote supervision of a general practitioner with special interest in dermatology. *Clin Exp Dermatol.* 2011;36:489-494.
 64. Lowitt M, Kessler I, Kauffman C, Hooper F, Siegel E, Burnett J. Teledermatology and in-person examinations: a comparison of patient and physician perceptions and diagnostic agreement. *Arch Dermatol.* 1998;134:471-476.
 65. Williams T, May C, Esmail A, Ellis N. Patient satisfaction with store-and-forward teledermatology. *J Telemed Telecare.* 2001;7(Suppl 1):45-46.
 66. Qureshi A, Brandling-Bennett H, Wittenberg E, Chen S, Sober A, Kvedar J. Willingness-to-pay stated preferences for telemedicine versus in-person visits in patients with a history of psoriasis or melanoma. *Teamed J E Health.* 2006;12:639-643.
 67. May C, Giles L, Gupta G. Prospective observational comparative study assessing the role of store and forward teledermatology triage in skin cancer. *Clin Exp Dermatol.* 2008;33:736-739.
 68. Ferrandiz L, Moreno-Ramirez D, Nieto-Garcia A, et al. Teledermatology-based presurgical management for nonmelanoma skin cancer: a pilot study. *Dermatol Surg.* 2007;33:1092-1098.

69. Ludwick DA, Lortie C, Doucette J, Rao J, Samoil-Schelstraete C. Evaluation of a telehealth clinic as a means to facilitate dermatologic consultation: pilot project to assess the efficiency and experience of teledermatology used in a primary care network. *J Cutan Med Surg.* 2010;14:7-12.
70. Edison KE, Fleming DA, Nieman EL, Stine K, Chance L, Demiris G. Content and style comparison of physician communication in teledermatology and in-person visits. *Teemed J E Health.* 2013;19:509-514.
71. Delfino M, Holt EW, Taylor CR, Wittenberg E, Qureshi A. Willingness-to-pay stated preferences for 8 health-related quality-of-life domains in psoriasis: a pilot study. *J Am Acad Dermatol.* 2008;59:439-447.
72. Whited JD, Warshaw EM, Edison KE, et al. Effect of store and forward teledermatology on quality of life: a randomized controlled trial. *JAMA Dermatol.* 2013;149:584-591.
73. Ebner C, Wurm EM, Binder B, et al. Mobile teledermatology: a feasibility study of 58 subjects using mobile phones. *J Telemed Telecare.* 2008;14:2-7.
74. Eminović N, Witkamp L, de Keizer NF, Wyatt JC. Patient perceptions about a novel form of patient-assisted teledermatology. *Arch Dermatol.* 2006;142:647-651.
75. Moreno-Ramirez D, Ferrandiz L, Bernai A, Duran R, Martin J, Camacho F. Teledermatology as a filtering system in pigmented lesion clinics. *J Telemed Telecare.* 2005;11:298-303.
76. Van der Heijden JP, de Keizer NF, Bos JD, Spuls PI, Witkamp L. Teledermatology applied following patient selection by general practitioners in daily practice improves efficiency and quality of care at lower cost. *Br J Dermatol.* 2011;165:1058-1065.
77. Chambers C, Parsi K, Schupp C, Armstrong A. Patient-centered online management of psoriasis: a randomized controlled equivalency trial. *J Am Acad Dermatol.* 2012;66:948-953.
78. Parsi K, Chambers CJ, Armstrong AW. Cost-effectiveness analysis of a patient-centered care model for management of psoriasis. *J Am Acad Dermatol.* 2012;66:563-570.
79. Bergman H, Tsai KY, Seo SJ, Kvedar JC, Watson AJ. Remote assessment of acne: the use of acne grading tools to evaluate digital skin images. *Teemed J E Health.* 2009;15:427-430.
80. Qureshi A, Brandling-Bennett H, Giberti S, McClure D, Halpern E, Kvedar J. Evaluation of digital skin images submitted by patients who received practical training or an online tutorial. *J Telemed Telecare.* 2006;12:79-82.
81. Eminović N, Witkamp L, Ravelli AC, et al. Potential effect of patient-assisted teledermatology on outpatient referral rates. *J Telemed Telecare.* 2003;9:321-327.
82. Boyce Z, Gilmore S, Xu C, Soyer HP. The remote assessment of melanocytic skin lesions: a viable alternative to face-to-face consultation. *Dermatology.* 2011;223:244-250.
83. Koller S, Hofmann-Wellenhof R, Hayn D, Weger W, Kästner P, Schreier G. Teledermatological monitoring of psoriasis patients on biologic therapy. *Acta Derm Venereol.* 2011;91:680-685.
84. Fröhlauf J, Schwantzer G, Ambros-Rudolph CM, et al. Pilot study on the acceptance of mobile teledermatology for the home monitoring of high-need patients with psoriasis. *Australas J Dermatol.* 2012;53:41-46.
85. Balato N, Megna M, Di Costanzo L, Balato A, Ayala F. Educational and motivational support service: a pilot study for mobile-phone-based interventions in patients with psoriasis. *Br J Dermatol.* 2013;168:201-205.
86. Bergstrom K. MelaFind is approved by the FDA: where does it fit in dermatology? *J Drugs Dermatol.* 2012;11:420-422.
87. World Health Organization. *Telemedicine: opportunities and developments in member states.* Geneva, Switzerland: World Health Organization; 2010. pp. 1-96.
88. Bashshur RL, Shannon GW. *History of telemedicine.* New Rochelle (NY): Mary Ann Liebert, Inc; 2009. pp. 415-484.
89. Armstrong AW, Wu J, Kovarik CL, Goldyne ME. State of teledermatology programs in the United States. *J Am Acad Dermatol.* 2012;67:939-944.
90. Desai B, McKoy K, Kovarik C. Overview of international teledermatology. *Pan Afr Med J.* 2010;20:1-14.
91. Barbieri JS, Nelson CA, James WD, et al. The reliability of teledermatology to triage inpatient dermatology consultations. *JAMA Dermatol.* 2014;150:1-6.
92. Gordon J. Dermatologic assessment from a distance: the use of teledermatology in an outpatient chemotherapy infusion center. *Clin J Oncol Nurs.* 2012;16:418-420.
93. Gordon J, Gruber M. An innovative off-campus infusion suite designed to improve experiences of patients with cancer. *Clin J Oncol Nurs.* 2012;16:354-359.
94. Chen TS, Goldyne ME, Mathes EF, Frieden IJ, Gilliam AE. Pediatric teledermatology: observations based on 429 consults. *J Am Acad Dermatol.* 2010;62:61-66.
95. Philp JC, Cordoro KM, Frieden IJ. Pediatric teledermatology consultations: relationship between provided data and diagnosis. *Pediatr Dermatol.* 2013;30:561-567.
96. Craiglow BG, Resneck JS, Lucky AW, et al. Pediatric dermatology workforce shortage: perspectives from academia. *J Am Acad Dermatol.* 2008;59:986-989.
97. Chanussot-Deprez C, Contreras-Ruiz J. Telemedicine in wound care: a review. *Adv Skin Wound Care.* 2013;26:78-82.
98. Braun RP, Vecchietti JL, Thomas L, et al. Telemedical wound care using a new generation of mobile telephones. *Arch Dermatol.* 2005;141:254-258.
99. Salmhofer W, Hofmann-Wellenhof R, Gabler G, et al. Wound teleconsultation in patients with chronic leg ulcers. *Dermatology.* 2005;210:211-217.
100. Binder B, Hofmann-Wellenhof R, Salmhofer W, Okcu W, Kerl H, Soyer HP. Teledermatological monitoring of leg ulcers in cooperation with home care nurses. *Arch Dermatol.* 2007;143:1511-1514.
101. Pak HS. Teledermatology and teledermatopathology. *Semin Cutan Med Surg.* 2002;21:179-189.
102. Hart J. The visual nature of dermatology is a good match for telemedicine. *Teemed J E Health.* 2011;17:405-408.
103. Henning JS, Wohltmann W, Hivnor C. Teledermatology from a combat zone. *Arch Dermatol.* 2010;146:676-677.
104. American Academy of Dermatology web site. Military dermatologists treat troops, provide humanitarian missions abroad. Available at: <http://www.aad.org/dw/monthly/2012/october/military-dermatologists-treat-troops-provide-humanitarian-missions-abroad#allpages>. Accessed August 1, 2013.
105. American Telemedicine Association web site. U.S. teledermatology survey 2012. Available at: <http://www.american-telemed.org/docs/default-source/member-groups/current-active-teledermatology-programs.pdf?sfvrsn=0>. Accessed August 1, 2013.
106. American Academy of Dermatology Association web site. AADA position statement on telemedicine. Available at: <http://www.aad.org/forms/policies/Uploads/PS/PS-Telemedicine6-15-07.pdf>. Accessed September 1, 2014.
107. Armstrong A, Kwong MW, Ledo L, Nesbitt TS, Shewry SL. Practice models and challenges in teledermatology: a study

- of collective experiences from teledermatologists. *PLoS One*. 2011;6:e28687.
108. American Academy of Dermatology web site. AccessDerm teledermatology program. Available at: <http://www.aad.org/members/volunteer-and-mentor-opportunities/accessdermatology-program>. Accessed September 7, 2013.
 109. Hu J, Masenga EJ, Sethi A, Craft N. Dermatology and HIV/AIDS in Africa. *J Glob Infect Dis*. 2011;3:275-280.
 110. Afsar FS. Skin infections in developing countries. *Curr Opin Pediatr*. 2010;22:459-466.
 111. Tsang MW, Kovarik CL. Global access to dermatopathology services: physician survey of availability and needs in sub-Saharan Africa. *J Am Acad Dermatol*. 2010;63:345-346.
 112. Colven R, Shim MHM, Brock D, Todd G. Dermatological diagnostic acumen improves with use of a simple telemedicine system for underserved areas of South Africa. *Telemed J E Health*. 2011;17:363-369.
 113. Hay R, Bendeck SE, Chen S, et al. Skin disease. In: Jamison DT, Breman JG, Measham AR, et al., eds. *Disease control priorities in developing countries*. 2nd ed. Washington (DC): World Bank; 2006. pp. 707-722.
 114. Frühauf J, Hofmann-Wellenhof R, Kovarik C, et al. Mobile teledermatology in sub-Saharan Africa: a useful tool in supporting health workers in low-resource centres. *Acta Derm Venereol*. 2013;93:106-107.
 115. University of Washington web site. Colven R. A teledermatology network for underserved areas of South Africa. Available at: <http://faculty.washington.edu/rcolven/teledermatology.shtml>. August 7, 2013.
 116. Africa Teledermatology Project web site. Africa teledermatology project. Available at: <http://africa.telederm.org/>. Accessed August 5, 2013.
 117. Weinberg J, Kaddu S, Gabler G, Kovarik C. The African Teledermatology Project: providing access to dermatologic care and education in sub-Saharan Africa. *Pan Afr Med J*. 2009;3:1-12.
 118. Chang AY, Kovarik CL. Providing dermatologic care in Botswana. *Pan Afr Med J*. 2011;7:1-2.
 119. Azfar RS, Lee RA, Castelo-Soccio L, et al. Reliability and validity of mobile teledermatology in human immunodeficiency virus-positive patients in Botswana: a pilot study. *JAMA Dermatol*. 2014;150:8-10.
 120. Williams CM, Kedar I, Smith L, Brandling-Bennett HA, Lugn N, Kvedar JC. Teledermatology education for internal medicine residents. *J Am Acad Dermatol*. 2005;52:1098-1099.
 121. McFarland LV, Raugi GJ, Taylor LL, Reiber GE. Implementation of an education and skills programme in a teledermatology project for rural veterans. *J Telemed Telecare*. 2012;18:66-71.
 122. Chang AY, Ghose S, Littman-Quinn R, et al. Use of mobile learning by resident physicians in Botswana. *Telemed J E Health*. 2012;18:11-13.
 123. van der Heijden JP, Spuls PI, Voorbraak FP, de Keizer NF, Witkamp L, Bos JD. Tertiary teledermatology: a systematic review. *Telemed J E Health*. 2010;16:56-62.
 124. Burg G, Hasse U, Cipolat C, et al. Teledermatology: just cool or a real tool? *Dermatology*. 2005;210:169-173.
 125. Scheinfeld N. The use of teledermatology to supervise dermatology residents. *J Am Acad Dermatol*. 2005;52:378-380.
 126. Introcaso CE, Kovarik CL. Dermatology in Botswana: the American Academy of Dermatology's resident international grant. *Dermatol Clin*. 2011;29:63-67.
 127. Lozzi GP, Soyer HP, Massone C, et al. The additive value of second opinion teleconsulting in the management of patients with challenging inflammatory, neoplastic skin diseases: a best practice model in dermatology? *J Eur Acad Dermatol Venereol*. 2007;21:30-34.
 128. American Academy of Dermatology web site. Dermatology workforce resources and physician distribution map. Available at: <http://www.aad.org/DermDensity/view.aspx>. Accessed September 25, 2013.

Teledermatology: From historical perspective to emerging techniques of the modern era

Part II: Emerging technologies in teledermatology, limitations and future directions

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Learning objectives

After completing this learning activity, participants should be able to discuss technologies within the field of teledermatology, including mobile teledermatology, teledermoscopy, and teledermatopathology; describe the current status of teledermatology research that supports the use of these emerging technologies; characterize the major technical, legal, and ethical limitations of teledermatology; and discuss potential future applications of teledermatology.

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Telemedicine is the use of telecommunications technology to support health care at a distance. Dermatology relies on visual cues that are easily captured by imaging technologies, making it ideally suited for this care model. Advances in telecommunications technology have made it possible to deliver high-quality skin care when patient and provider are separated by both time and space. Most recently, mobile devices that connect users through cellular data networks have enabled teledermatologists to instantly communicate with primary care providers throughout the world. The availability of teledermoscopy provides an additional layer of visual information to enhance the quality of teleconsultations. Teledermatopathology has become increasingly feasible because of advances in digitization of entire microscopic slides and robot-assisted microscopy. Barriers to additional expansion of these services include underdeveloped infrastructure in remote regions, fragmented electronic medical records, and varying degrees of reimbursement. Teleconsultants also confront special legal and ethical challenges as they work toward building a global network of practicing physicians. (*J Am Acad Dermatol* 2015;72:577-86.)

Key words: Internet; smartphone; store-and-forward; teledermatology; teledermatopathology; teledermoscopy.

INTRODUCTION

In part I of this continuing medical education article, we reviewed the rationale for teledermatology (TD) as a means for providing care to previously

underserved patient populations. Technological advances have made high-quality, remote diagnosis increasingly feasible by affording dermatologists the ability to assess standard and dermoscopic images of

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Abbreviations used:

HIT:	health care information technology
RCM:	reflectance confocal microscopy
RT:	real-time
S&F:	store-and-forward
TD:	teledermatology
TDP:	teledermatopathology
VSS:	virtual slide system

skin lesions. In addition, the availability of remote histopathology analysis as an adjunct TD tool may provide greater certainty to diagnoses rendered remotely. Although these advances suggest a promising future for practicing teledermatologists, there remain several practical barriers to further implementation of these services, discussed herein.

EMERGING TECHNOLOGIES

Mobile teledermatology

Key points

- Smartphones are well-suited to teledermatology
- In developing countries, smartphones are more available and reliable than other electronic communication platforms

The feasibility of mobile devices as TD tools is established in the literature.¹⁻¹³ Mobile TD empowers patients to play an active role by sending images and histories from home.¹⁻⁶ This approach is particularly well-suited for chronic conditions, such as psoriasis, that require frequent follow-up to optimize therapy. Smartphones, which are cellular phones that perform many functions typical of computers, including access to the Internet, have also been used to track wound healing and evaluate patients at skin cancer screening events.^{7,8}

Smartphone-captured images have yielded diagnostic agreement between in-person dermatologists and teleconsultants in 61% to 80% of cases^{6,7,9-13}; management concordance has ranged from 81% to 98%.^{7,13,14} In an Austrian study, investigators determined that teledermatologists could have treated 53% to 59% of cases without the need for in-person visits.⁹

The increasing number of mobile phone users in the developing world makes these devices an ideal TD platform.¹⁵ Studies of mobile TD in Egypt and Ghana found diagnostic agreement between in-person dermatologists and teleconsultants in 75% and 78% to 79% of cases, respectively.^{16,17} Mobile TD supports practitioners in Uganda, where 76% of patients in a pilot study were managed satisfactorily; none reported symptom worsening.¹⁸

If privacy was guaranteed, Botswanan patients were satisfied and willing to wait for TD rather than travel and miss work.¹⁹

Smartphones have been less useful as platforms for viewing cases; in most studies, teledermatologists evaluate images using computer screens. Recently, handheld tablets were found to be superior to smartphones for image analysis.²⁰

Teledermoscopy

Key points

- Teledermoscopy may improve the diagnostic accuracy of teledermatology
- New mobile applications promote patient-assisted teledermoscopy, in which patients capture images and send them directly to physicians
- Limitations include high costs and a steep learning curve

Early studies found that dermoscopy use by experienced examiners increased the accuracy of melanoma diagnoses by 49% versus clinical diagnosis based on naked eye visualization alone.²¹ Inexperienced examiners using dermoscopy achieved less accuracy.²¹⁻²³ Teledermoscopy may be used in conjunction with any TD modality. Investigators have found high interobserver concordance after addition of dermoscopy to standard images.²⁴⁻²⁹ The accuracy of teledermoscopic diagnoses based on histopathology has ranged from 75% to 95%,^{22,23,25,26,30-33} with teledermoscopy reportedly increasing accuracy by 15% compared to clinical images alone.³⁴

Teledermoscopy has gained support as a tool for triaging TD consults. In 1 study, teledermoscopy approached 100% sensitivity and 90% specificity for melanoma and nonmelanoma skin cancer detection, and half of patients were manageable without a follow-up visit or procedure.³⁵ Other investigators found a 2-step approach, in which clinical images were first assessed to determine need for dermoscopy, useful for reliably telediagnosing patients with pigmented lesions in poorly visible body sites.³⁶

Smartphone dermoscopy attachments have been developed. Using the iPhone 4 (Apple Inc, Cupertino, CA) to capture images, investigators in 1 study found accuracies of 50.7% to 60.9%, based on histopathology, for TD with dermatoscopic images, compared to 66.7% for in-person dermatology with dermoscopy.³¹ These values were lower than findings in previous teledermoscopy studies.³¹ Another study found no advantage to mobile teledermoscopy compared to standard store-and-forward (S&F) TD and, interestingly, S&F TD was

slightly superior to teledermoscopy for making a detailed diagnosis, particularly for benign and malignant nonmelanocytic lesions.³²

Teledermoscopy lengthens the time to prepare consult data and is more expensive, consuming 50% more time and 2.4 times more money than standard photography in 1 study.²⁵ Reliability depends upon user experience. In 1 study, clinical histories greatly increased the accuracy of dermatoscopic diagnosis for novices, but did not influence the high accuracy achieved by experts.²² Use of dermoscopy for self-diagnosis of suspicious lesions by motivated patients at increased risk for developing melanoma has been described^{37,38}; however, high costs of these instruments and the steep learning curve associated with interpreting images may limit their use for self-skin examinations.³⁷

Additional noninvasive imaging modalities

Key points

- Novel technologies may enable more objective evaluation of atypical pigmented lesions
- These may be used as adjunct tools in teledermatology, particularly by dermatologists caring for high-risk patient populations requiring frequent follow-up

Novel technologies, such as MelaFind, were designed to assist dermatologists in making biopsy decisions when confronted with atypical pigmented skin lesions. In 2011, the US Food and Drug Administration (FDA) approved MelaFind for this purpose.^{39,40} The technology works by scanning pigmented lesions in 10 distinct spectral bands between infrared (950 nm) and blue (430 nm) regions of the electromagnetic spectrum.⁴¹ In a multicenter, prospective, blinded study, dermatologists using MelaFind were found to have a 98.4% sensitivity for detecting thin melanomas and borderline pigmented lesions, using skin biopsy as the criterion standard.⁴¹ Compared to MelaFind, diagnostic sensitivity was lower for in-person dermatologists using dermoscopy alone, and, moreover, there was high interobserver variability among in-person physicians, suggesting that MelaFind may substantially improve the diagnosis of atypical pigmented lesions.⁴¹ This trial could not detect the true sensitivity of dermatologists using MelaFind because any melanomas not scheduled for biopsy would not be considered. The specificity of MelaFind was also significantly superior to that of in-person clinicians, measured at 9.9% versus 3.7%, respectively ($P = .02$).⁴¹ However, because only pigmented lesions scheduled for biopsy procedures

could be used to determine specificity, these specificity values were not believed to be generalizable to the general population.⁴¹ A second, smaller study of 47 pigmented lesions corroborated the high sensitivity (22 of 23 [96%] of biopsy specimens [95% lower confidence bound, 0.83]) of MelaFind, but reported a markedly lower specificity (2 of 24 [8%] of biopsy specimens were actually malignant melanomas [95% confidence interval, 0.01-0.25]) for MelaFind compared to the aforementioned trial.⁴² Investigators concluded that MelaFind is a highly sensitive tool for guiding dermatologists in their decision to obtain biopsy specimens of suspicious pigmented lesions, but may result in higher rates of biopsy for skin lesions that are actually benign.⁴²

In vivo reflectance confocal microscopy (RCM) is another noninvasive imaging tool used to evaluate pigmented lesions.⁴³ RCM uses low-energy lasers to view sequential layers of the epidermis and papillary dermis, a technique known as optical sectioning.⁴³ The resolution of the generated images is comparable with that of standard 5- μm pathology sections, and as such, RCM has been lauded as having the potential to provide a “virtual biopsy” of skin lesions.⁴³ These technologies are being employed in clinical trials to evaluate melanoma and nonmelanoma skin cancer.³⁹ RCM diagnoses may also be automated, which may enhance the objectivity of rendering melanoma diagnoses. Using RCM equipment is associated with a steep learning curve and therefore user-dependent.⁴³ RCM is also limited by high upfront costs.⁴³

Dermatoscopic tools such as MoleMax, EasyScan, and FotoFinder have built-in software that allows physicians to objectively evaluate changes in patients’ skin lesions over time.³⁹ The advantages of these and other imaging modalities may include reduced skin biopsy rates, which may be cost-saving in addition to lowering patient morbidity.³⁹ While few studies have been conducted using these advanced imaging technologies to evaluate patients situated remotely, their ability to improve the objectivity of diagnosing potentially dangerous skin lesions suggests utility for practitioners of TD.

Teledermatopathology

Key points

- The diagnostic criterion standard of histopathology is not universally available
- There are multiple modalities for providing pathologic analysis remotely

The integral role of dermatopathology for diagnosing many types of skin lesions makes it challenging to practice at a distance using clinical

Table I. Advantages and disadvantages of teledermatopathology modalities

	S&F method*		
	Static image	Virtual slide	RT
Advantages	<ul style="list-style-type: none"> Convenient (most microscopes are equipped with camera technology) Less expensive Does not generally require high bandwidth 	<ul style="list-style-type: none"> Permits viewing of the entire field, correcting for inadequate field selection in static S&F Ability to view entire slide is more conducive to TDP educational endeavors 	<ul style="list-style-type: none"> Most closely approximates traditional pathologic examination Allows pathologists to immediately conference with clinicians
Disadvantages	<ul style="list-style-type: none"> Fields viewed are limited to those imaged Limited utility for lesions in which subtle architectural changes must be appreciated for diagnosis (eg, inflammatory disorders or dysplastic nevi) Remote assessment may depend on formulation of a complete differential diagnosis by referring provider 	<ul style="list-style-type: none"> Requires expensive hardware and software Image influenced by stain quality and slide positioning Slide preparation requires more time, resulting in a slower turnaround Limited utility for the diagnosis of inflammatory dermatoses 	<ul style="list-style-type: none"> Requires a high bandwidth capability Requires expensive software and hardware Unavailability of maintenance personnel Challenging for those practicing across multiple time zones Poorer image resolution compared to static images

RT, Real-time; S&F, store-and-forward; TDP, teledermatopathology.

*S&F TDP may scan a single image of a slide (static image) or scan the entire slide (virtual slide).⁴⁴⁻⁴⁷

images alone.¹⁵ Table I describes features of each teledermatopathology (TDP) modality.⁴⁴⁻⁴⁷ Early efforts to serve patients living in locations where there were no dermatopathologists involved remote biopsy acquisition with subsequent analysis at distant sites—not unlike what is currently done in the standard outpatient setting, albeit across far greater distances. Investigators used this method in the African Teledermatology Project to show that telediagnoses were histologically accurate in 58% of the most challenging cases.⁴⁸ Static scanned slide images enable high telediagnostic concordance that approximates conventional dermatopathology,⁴⁹⁻⁵¹ but in some studies concordance improves after adding standard microscopy because static images are susceptible to inaccurate field selection.^{51,52} Virtual slide systems (VSSs) digitalize entire slides at high resolution, enabling any aspect to be remotely analyzed.⁴⁷ This is reliable for pigmented lesions,⁵³ but was less successful for inflammatory disorders in one study.⁴⁷ In Japan, an integrated VSS has been developed that organizes clinical and pathologic data in an entirely online consultation system, allowing multiple experts at different locations and from a variety of medical specialties to contribute to diagnoses.⁵⁴ Investigators found that this was more convenient than conventional microscopy in terms of time and manpower, and feasible for use in settings with high-speed communication lines.⁵⁴

RT TDP is used in Botswana, where teledermatopathologists control microscopes remotely.⁵⁵

Particularly in resource-poor settings where dermatology is not a standard component of medical curricula, TDP may improve both clinical and educational outcomes.⁵⁵ While these methods have demonstrated high reliability, conventional microscopy typically generates higher interobserver diagnostic concordance among pathologists and also consumes less time compared to pathologists assessing virtual versions of tissue specimens.^{56,57} A recent pilot study found that smartphones (iPhone 4s [Apple Inc]) attached to microscopes were feasible TDP imagers.⁴⁶ Image analysis was performed using a tablet (iPad [Apple Inc]).⁴⁶ In the future, mobile devices may play a greater role in TDP. Currently, efforts are limited by the availability of personnel to process tissue and maintain equipment, high costs, and the regional reliability of electric power and high-speed Internet service.^{55,58}

LIMITATIONS OF TELEDERMATOLOGY

Some challenges to TD implementation reflect a nation's development status.⁵⁹ Limitations in developing countries include inadequate physical and technological infrastructure, while practitioners in developed countries face legal issues, limited reimbursement, market competition, and a perceived lack of demand.^{59,60} Legalities and ethics of TD practice are complicated because consults can be conducted over distances that span differing legal frameworks and conceptions of patients' rights. Table II summarizes some of the limitations of teledermatology, discussed in greater detail below.

Table II. Limitations of teledermatology

Limit type	Description of limits
Clinical	<ul style="list-style-type: none"> Physical touch, lost in TD, is important in diagnosing some skin conditions Use of TD for pigmented lesions may lead to underdetection of melanoma TD may not be able to replace full body skin examinations
Economic	<ul style="list-style-type: none"> There is limited federal reimbursement for store-and-forward TD TD may consume more time than in-person dermatology TD generates fewer lucrative procedures and follow-up appointments
Technological	<ul style="list-style-type: none"> Integration of TD with electronic medical records has been a challenge Incomplete global penetration of cellular data networks limits mobile TD Cost of mobile devices equipped with high-quality cameras remains high Inability to perform needed diagnostic or therapeutic interventions remotely
Legal	<ul style="list-style-type: none"> Most teledermatologists practice as consultants, such that the responsibility for medical decision-making remains that of referring providers TD technologies must achieve HIPAA-approved security capabilities
Ethical	<ul style="list-style-type: none"> Physical distance separates providers from the consequences of recommendations TD may promote technology-centric rather than patient-centric medicine International TD programs must be implemented in cooperation with local physicians and government agencies in order to avoid patient exploitation

HIPPA, Health Insurance Portability and Accountability Act; TD, teledermatology.

Clinical considerations

Key points

- Certain scenarios may be inappropriate for teledermatology, including the evaluation of pigmented lesions**
- Store-and-forward teledermatology should not entirely replace in-person encounters**

Some scenarios may not be appropriate for S&F TD, including full-body skin examinations, lesions in hair-bearing areas, melanocytic lesions in high-risk patients, and counseling.⁶¹ In addition, physical touch—absent in TD—is important for diagnosing skin diseases, such as actinic keratosis, psoriasis, and atopic dermatitis.^{62,63} Another study found that eczema cases were improperly evaluated and managed by dermatologists using RTTD.⁶³

Reliance on TD to assess pigmented lesions may lead to the underdetection of melanoma by general practitioners.⁶⁴⁻⁶⁶ Teledermoscopy reportedly improves the accuracy of remote melanoma diagnoses compared to clinical photographs alone^{35,67} but remains inferior to in-person encounters.⁶⁴ In 1 study, investigators found that 7 of 36 melanomas would have been misdiagnosed and mismanaged using TD alone.⁶⁴ Another study prospectively demonstrated a 33% rate of incidental melanoma discovery on patients referred by general practitioners to dermatologists for other suspicious lesions.⁶⁵ Yet another found that 9.8% of incidental lesions discovered after conventional referral from general practitioners were ultimately diagnosed as melanomas, while 78% of lesions suspicious for malignancy were ultimately benign based

solely on clinical judgments of dermatologists.⁶⁶ More recently, teledermatologists in the Pacific Northwest reported that melanomas diagnosed via TD had greater Breslow depth and were more likely to be invasive than those detected by face-to-face dermatology,⁶⁸ which contradicted the results of a previous study conducted in Spain.⁶⁹ In the latter, investigators found at the 9-year mark in a prospective study that patients with melanoma whose lesions were evaluated using TD, compared to conventional referral methods, had lesions with a better prognosis based on depth of invasion.⁶⁹ This nonrandomized study may have been subject to confounding variables, because primary care providers triaging patients to TD versus conventional referral may have been more likely to recommend in-person follow up for lesions with more concerning features.⁶⁹ For TD to be safe, nondermatologists must lower their threshold for suspicious lesions and be willing to conduct full-body skin examinations.⁷⁰

Economic considerations

Key points

- Comprehensive cost assessments of teledermatology are challenging**
- Reimbursement is cited as the foremost challenge to teledermatology expansion**
- Technological advances have continually reduced the direct costs of teledermatology**

Multiple studies support TD as a mechanism for reducing costs in particular clinical scenarios.⁷¹⁻⁷⁶ Reductions in referrals, lost employment, and travel time are all economic arguments supporting TD.^{72,73}

Calculated savings are proportional to in-person visit prevention and the distance to dermatology clinics.⁷⁴⁻⁷⁶ Savings are predicted for motivated patient populations and diseases characterized by ease of initial diagnosis, chronicity, and the need for frequent follow-up. In the Netherlands, which began funding TD in 2006 and where general practitioners use TD to determine need for in-person visits, investigators reported a significant drop in TD referrals that stabilized a year after initiating reimbursement in 2006. This may partially account for the observed cost reduction of 18% for TD versus conventional care.⁷⁷ Multiple studies support patient willingness to pay for teleconsultations.^{9,78} TD may provide additional cost savings compared to conventional care in the future, because equipment costs are falling and the economics of TD improves with higher consult volumes.^{75,76,79,80}

In 2011, the most frequently named challenge (71%) among Californian teledermatologists was obtaining reimbursement, and nearly 95% felt that financial incentives were needed to encourage additional participation.⁶¹ Others have pointed to competing sources of dermatologist revenue from more lucrative outpatient services.^{81,82} Many developed nations reimburse physicians for TD, but financial backing of TD efforts in the United States has moved more slowly.^{59,77,83}

As of 2013, Medicare reimbursed S&F TD in Alaska and Hawaii, and covered RTTD country-wide.⁸⁴ As of 2011, Medicaid reimburses telehealth in 39 states, although allocation is determined by individual states.^{81,85} Private insurers increasingly reimburse for TD services rendered to isolated populations.⁸¹ While payments are comparable to in-person care, time spent on TD may result in income loss because procedures cannot be performed remotely.⁸¹ In addition, TD patients are typically billed for fewer services and have less frequent follow-up visits.⁸⁶ This means that while sustainability requires adequate and universal reimbursement, remuneration may be insufficient to recruit clinicians away from standard practice. As discussed in detail below, the Patient Protection and Affordable Care Act (PPACA) of 2010 may have shifted existing health care delivery and payment structures, such that this fee-for-service mentality among individual practitioners carries less weight in more integrated health care delivery systems.

Technological considerations

Key points

- Global access to cellular networks is not universal

- Image quality is linked to the accuracy of telediagnosis
- Mobile applications may contribute to the underdetection of serious skin conditions

Evidence suggests that electronic medical records (EMRs) and billing systems integration is an area in need of improvement.^{81,87,88} Smartphones remain expensive, and 30% of the global population cannot access even 3G data networks.⁸⁹ It is difficult to standardize smartphone-captured images, and the resolution of their cameras is often poorer than for typical stand-alone cameras, because sensors are smaller and less sensitive.⁸⁹ In a large prospective study, image quality was positively correlated with the telediagnostic accuracy.¹² In the developing world, reliance on smartphone cameras for telediagnosis may be problematic because of a health care workforce lacking formal photography training.⁹⁰ Younger patients send higher quality images and are more willing to pay for TD, suggesting a promising future for TD but raising questions about the utility of patient-assisted models for older populations.⁹¹

New mobile applications that provide automated diagnoses make reliability claims that may encourage the circumvention of routine care. Of the 229 dermatology-related mobile applications on the market as of late 2013, approximately 18% were intended for patients to use in self-surveillance or self-diagnosis.⁹² A recent study found that smartphone applications with computer algorithms designed to detect melanoma have low positive and negative predictive values.⁹³ Particularly when these tools are used at the discretion of patients, rather than as adjunct tools by dermatologists, they run the risk of obfuscating standard medical practice and may ultimately contribute to melanoma underdetection. In July 2011, the FDA announced plans to regulate applications that, if faulty, presented the greatest risks.^{93,94} In 2012, Congress passed the FDA Safety and Innovation Act, which allows regulation of some applications, although specifics have yet to be defined.⁹³

Legal considerations

Key points

- Patient security must remain a priority for teledermatologists
- Liability has been a minor concern for practitioners using the consultative model

In the consultative model, dermatologists give detailed recommendations based on histories and images, but implementation is the prerogative of referring providers.^{61,95} Compliance with the Health

Insurance Portability and Accountability Act (HIPAA) typically involves telling patients that their information will be transmitted electronically.⁹⁶ TD patients may suffer auditory or visual violations of confidentiality despite consultants' best efforts.⁹⁷ According to the American Academy of Dermatology Association Position Statement on Telemedicine (2004), providers should document understanding in a consent form and encrypt transmissions to secure protected health information (PHI).⁹⁶ Electronic mail is generally not considered safe—instead, information should be stored on a firewall-protected server.⁹⁸ Guidelines will evolve as technological advances transform health care information technology (HIT). Despite these challenges, no dermatologist as of 2011 had been successfully sued for services provided remotely.⁹⁵

Ethical considerations

Key points

- Achieving proper informed consent and preventing depersonalization are challenges
- Physicians practicing teledermatology across international borders must avoid patient exploitation

Several authors have discussed the ethical conundrums present in telemedicine.^{97,99-103} Support for TD is largely rooted in the notion that patients would otherwise be unable to see a specialist in person. Some have expressed concern that the routine use of TD may promote technology-centric rather than patient-centric medicine.⁹⁹ This argument is based upon concern that the user-friendly nature of mobile telemedicine encounters may tempt their use with as many patients as possible, regardless of whether consultation is necessary, such that teleconsults become means to financial ends.¹⁰⁰ Throughout history, physicians have expressed fear that a variety of technological advances may depersonalize the medical encounter. Perhaps this concern is most appropriately addressed via a thorough informed consent process in which patients uphold their autonomy over health care decision-making by confirming that they understand the benefits and risks associated with remote consultation.¹⁰⁰ Patients should understand which personnel will access their PHI and how information is stored, along with the benefits, risks, and alternatives to TD.¹⁰⁰

The extension of TD services to remote areas affords exciting opportunities for adventure-seeking physicians. For rural health care workers struggling to meet needs of local populations, it may be difficult to deny assistance from eager experts. Yet international TD may ultimately hinder the development of

specialist training in recipient nations. Efforts to ensure that education is at the core of TD will combat this tendency. The ultimate measure of a successful program is that consultations decline as local physicians acquire dermatologic acumen.

CONCLUSIONS

Key points

- Support for health care information technology is growing in light of health care reform
- Regulatory agencies face challenges to patient safety and privacy
- Teledermatology may mitigate health inequities and reduce the skin disease burden

A comprehensive telemedicine policy must promote the further development of HIT and address relevant ethical, legal, and financial issues.¹⁰⁴ One in 3 countries have telemedicine agencies, and 20% have national policies governing its use.⁵⁹ Although multiple agencies advocate for it, no federal policy governs telemedicine in the United States. As a consequence of PPACA, the US Government hopes that technology will play a larger role in reducing costs and improving outcomes. The federal government offered up to \$27 billion in incentives to providers who demonstrate meaningful use of EMR.⁷⁹ The Accountable Care Organization rule (2011) acknowledged telemedicine as a means to this end.⁷⁹ Although PPACA seeks to increase training for general practitioners and physician extenders, it did little to address specialty care shortages.⁷⁹ In this setting, TD is ripe for expansion.

TD has a promising future. The visual nature of skin disease and the relatively low acuity of many dermatologic illnesses have contributed to the success of TD to date. The additional development of mobile telecommunication may enhance medical education while providing a low-cost alternative for managing common skin conditions. The rise in patient-assisted TD suggests the possibility of more personal investments in health care, from self-monitoring of lesions with teledermoscopy to routine follow-up for chronic conditions using smartphones.⁸⁹ Regulatory agencies must assess the impact of technologies on clinical outcomes, and health care providers will confront the challenge of integrating TD with existing EMRs. The barriers presented by state-based licensure may be challenged as practitioners in rural areas become aware of the growing network of specialists eager to provide services. Rising skin cancer prevalence in conjunction with an aging population suggests a productive future for dermatologists.¹⁰⁵ TDP will

likely become a routine part of consults.⁸⁹ TD may address the needs of the elderly population, the severely ill, and those with limited mobility.^{99,106} TD uses rapidly expanding networks to facilitate health care access, improve patient satisfaction, and reduce the burden of skin disease.

REFERENCES

- Schreier G, Hayn D, Kastner P, Koller S, Salmhofer W, Hofmann-Wellenhof R. A mobile-phone based teledermatology system to support self-management of patients suffering from psoriasis. *Conf Proc IEEE Eng Med Biol Sci.* 2008;2008:5338-5341.
- Balato N, Megna M, Di Costanzo L, Balato A, Ayala F. Educational and motivational support service: a pilot study for mobile-phone-based interventions in patients with psoriasis. *Br J Dermatol.* 2013;168:201-205.
- Frühauf J, Schwantzer G, Ambros-Rudolph CM, et al. Pilot study using teledermatology to manage high-need patients with psoriasis. *Arch Dermatol.* 2010;146:200-201.
- Koller S, Hofmann-Wellenhof R, Hayn D, Weger W, Kästner P, Schreier G. Teledermatological monitoring of psoriasis patients on biologic therapy. *Acta Derm Venereol.* 2011;91:680-685.
- Frühauf J, Schwantzer G, Ambros-Rudolph CM, et al. Pilot study on the acceptance of mobile teledermatology for the home monitoring of high-need patients with psoriasis. *Australas J Dermatol.* 2012;53:41-46.
- Boyce Z, Gilmore S, Xu C, Soyer HP. The remote assessment of melanocytic skin lesions: a viable alternative to face-to-face consultation. *Dermatology.* 2011;223:244-250.
- Lamel S, Haldeman K, Ely H, Kovarik C, Pak H, Armstrong A. Application of mobile teledermatology for skin cancer screening. *J Am Acad Dermatol.* 2012;67:576-581.
- Braun RP, Vecchietti JL, Thomas L, et al. Telemedical wound care using a new generation of mobile telephones. *Arch Dermatol.* 2005;141:254-258.
- Ebner C, Wurm EM, Binder B, Kittler H, Lozzi GP, Massone C, et al. Mobile teledermatology: a feasibility study of 58 subjects using mobile phones. *J Telemed Telecare.* 2008;14:2-7.
- Massone C, Lozzi GP, Wurm E, et al. Personal digital assistants in teledermatology. *Br J Dermatol.* 2006;154:801-802.
- Shin H, Kim DH, Ryu HH, Yoon SY, Jo SJ. Teledermatology consultation using a smartphone multimedia messaging service for common skin diseases in the Korean army: a clinical evaluation of its diagnostic accuracy. *J Telemed Telecare.* 2014;20:70-74.
- Weingast J, Scheibböck C, Wurm EM, et al. A prospective study of mobile phones for dermatology in a clinical setting. *J Telemed Telecare.* 2013;19:213-218.
- Kaliyadan F, Amin TT, Kuruvilla J, Ali WH. Mobile teledermatology—patient satisfaction, diagnostic and management concordance, and factors affecting patient refusal to participate in Saudi Arabia. *J Telemed Telecare.* 2013;19:315-319.
- Börve A, Holst A, Gente-Lidholm A, Molina-Martinez R, Paoli J. Use of the mobile phone multimedia messaging service for teledermatology. *J Telemed Telecare.* 2012;18:292-296.
- Massone C, Wurm EM, Hofmann-Wellenhof R, Soyer HP. Teledermatology: an update. *Semin Cutan Med Surg.* 2008;27:101-105.
- Tran K, Ayad M, Weinberg J, et al. Mobile teledermatology in the developing world: implications of a feasibility study on 30 Egyptian patients with common skin diseases. *J Am Acad Dermatol.* 2011;64:302-309.
- Osei-Tutu A, Shih T, Rosen A, et al. Mobile teledermatology in Ghana: sending and answering consults via mobile platform. *J Am Acad Dermatol.* 2013;69:e90-e91.
- Frühauf J, Hofmann-Wellenhof R, Kovarik C, et al. Mobile teledermatology in sub-Saharan Africa: a useful tool in supporting health workers in low-resource centres. *Acta Derm Venereol.* 2013;93:106-107.
- Azfar RS, Weinberg JL, Cavric G, Lee-Keltner IA, Bilker WB, Gelfand JM, et al. HIV positive patients in Botswana state that mobile teledermatology is an acceptable method for receiving dermatology care. *J Telemed Telecare.* 2011;17:338-340.
- Brandt R, Hensley D. Teledermatology: the use of ubiquitous instruction, collaboration, and consultation. *J Clin Aesthet Dermatol.* 2012;5:35-37.
- Kittler H, Pehamberger H, Solff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* 2002;3:159-165.
- Blum A, Hofmann-Wellenhof R, Luedtke H, et al. Value of the clinical history for different users of dermoscopy compared with results of digital image analysis. *J Eur Acad Dermatol Venereol.* 2004;18:665-669.
- Piccolo D, Smolle J, Argenziano G, et al. Teledermoscopy - results of a multicentre study on 43 pigmented skin lesions. *J Telemed Telecare.* 2000;6:132-137.
- Provost N, Kopf AW, Rabinovitz HS, et al. Comparison of conventional photographs and telephonically transmitted compressed digitized images of melanomas and dysplastic nevi. *Dermatology.* 1998;196:299-304.
- Moreno-Ramirez D, Ferrandiz L, Galdeano R, Camacho FM. Teledermatoscopy as a triage system for pigmented lesions: a pilot study. *Clin Exp Dermatol.* 2006;31:13-18.
- Senel E, Baba M, Durdu M. The contribution of teledermatoscopy to the diagnosis and management of non-melanocytic skin tumours. *J Telemed Telecare.* 2013;19:60-63.
- Wohltmann W, Lappan C, Henning S. Teledermoscopy of pigmented lesions: a pilot study [abstract]. *J Am Acad Dermatol.* 2011;64:AB76.
- Sheraz A, Halpern S. Influence of additional dermoscopy images on teledermatology screening of skin lesions. *Br J Dermatol.* 2011;165:136.
- Fabbrocini G, Balato A, Rescigno O, Mariano M, Scalvenzi M, Brunetti B. Telediagnosis and face-to-face diagnosis reliability for melanocytic and non-melanocytic "pink" lesions. *J Eur Acad Dermatol Venereol.* 2008;22:229-234.
- Ferrara G, Argenziano G, Cerroni L, et al. A pilot study of a combined dermoscopic-pathological approach to the telediagnosis of melanocytic skin neoplasms. *J Telemed Telecare.* 2004;10:34-38.
- Börve A, Terstappen K, Sandberg C, Paoli J. Mobile teledermoscopy—there's an app for that!. *Dermatol Pract Concept.* 2013;3:41-48.
- Kroemer S, Frühauf J, Campbell T, Massone C. Mobile teledermatology for skin tumour screening: diagnostic accuracy of clinical and dermoscopic image tele-evaluation using cellular phones. *Br J Dermatol.* 2011;164:973-979.
- Piccolo D, Smolle J, Wolf I, et al. Face-to-face diagnosis vs telediagnosis of pigmented skin tumors. *Arch Dermatol.* 1999;135:1467-1471.
- Warshaw EM, Hillman YJ, Greer NL, et al. Teledermatology for diagnosis and management of skin conditions: a systematic review. *J Am Acad Dermatol.* 2011;64:759-772.
- Tan E, Yung A, Jameson M, Oakley A, Rademaker M. Successful triage of patients referred to a skin lesion clinic

- using teledermoscopy (IMAGE IT trial). *Br J Dermatol.* 2010; 162:803-811.
36. Di Stefani A, Zalaudek I, Argenziano G, Chimenti S, Soyer HP. Feasibility of a two-step teledermatologic approach for the management of patients with multiple pigmented skin lesions. *Dermatol Surg.* 2007;33:686-692.
 37. Goulart JM, Malvehy J, Puig S, Martin G, Marghoob AA. Dermoscopy in skin self-examination. *Arch Dermatol.* 2011; 147:53-58.
 38. Janda M, Loescher L, Soyer HP. Enhanced skin self-examination: a novel approach to skin cancer monitoring and follow-up. *JAMA Dermatol.* 2013;149:231-236.
 39. Bergstrom K. MelaFind is approved by the FDA: where does it fit in dermatology? *J Drugs Dermatol.* 2012;11:420-422.
 40. US Food and Drug Administration Department of Health and Human Services website. Foreman C. The Center for Devices and Radiological Health (CDRH) acceptance letter for premarket approval for MelaFind (November 1, 2011). Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf9/p090012a.pdf. Accessed September 24, 2014.
 41. Monheit G, Cognetta AB, Ferris L, et al. The performance of MelaFind: a prospective multicenter study. *Arch Dermatol.* 2011;147:188-194.
 42. Martires KJ, Barnholtz-Sloan JS. Comparison of diagnostic and management sensitivity to melanoma between dermatologists and MelaFind: a pilot study. *Arch Dermatol.* 2012;148:1083-1084.
 43. Ferris LK, Harris RJ. New diagnostic aids for melanoma. *Dermatol Clin.* 2012;30:535-545.
 44. Pak HS. Teledermatology and teledermatopathology. *Semin Cutan Med Surg.* 2002;21:179-189.
 45. Massone C, Brunasso AM, Campbell TM, Soyer HP. State of the art of teledermatopathology. *Am J Dermatopathol.* 2008; 30:446-450.
 46. Lehman JS, Gibson LE. Smart teledermatopathology: a feasibility study of novel, high-value, portable, widely accessible and intuitive telepathology methods using handheld electronic devices. *J Cutan Pathol.* 2013;40:513-518.
 47. Massone C, Soyer HP, Lozzi GP, et al. Feasibility and diagnostic agreement in teledermatopathology using a virtual slide system. *Hum Pathol.* 2007;38:546-554.
 48. Tsang MW, Kovarik CL. The role of dermatopathology in conjunction with teledermatology in resource-limited settings: lessons from the African Teledermatology Project. *Int J Dermatol.* 2011;50:150-156.
 49. Weinstein LJ, Epstein JI, Edlow D, Westra WH. Static image analysis of skin specimens: the application of telepathology to frozen section evaluation. *Hum Pathol.* 1997;28:30-35.
 50. Dawson P, Johnson J, Edgemon L, Brand C, Hall E. Outpatient frozen sections by telepathology in a Veterans Administration medical center. *Hum Pathol.* 2000;31:786-788.
 51. Piccolo D, Soyer H, Burgdorf W, et al. Concordance between telepathologic diagnosis and conventional histopathologic diagnosis: a multiobserver store-and-forward study on 20 skin specimens. *Arch Dermatol.* 2002;138:53-58.
 52. Berman B, Elgart G, Burdick A. Dermatopathology via a still-image telemedicine system: diagnostic concordance with direct microscopy. *Telemed J.* 1997;3:27-32.
 53. Okada DH, Binder SW, Felten CL, Strauss JS, Marchevsky AM. "Virtual microscopy" and the internet as telepathology consultation tools: diagnostic accuracy in evaluating melanocytic skin lesions. *Am J Dermatopathol.* 1999;21:525-531.
 54. Nakayama I, Matsumura T, Kamataki A, et al. Development of a teledermatopathology consultation system using virtual slides. *Diagn Pathol.* 2012;7:1-9.
 55. Fischer MK, Kayembe MK, Scheer AJ, Introcaso CE, Binder SW, Kovarik CL. Establishing telepathology in Africa: lessons from Botswana. *J Am Acad Dermatol.* 2011;64: 986-987.
 56. Morgan MB, Tannenbaum M, Smoller BR. Telepathology in the diagnosis of routine dermatopathologic entities. *Arch Dermatol.* 2003;139:637-640.
 57. Riedl E, Asgari M, Alvarez D, Margaritescu I, Gottlieb GJ. A study assessing the feasibility and diagnostic accuracy of real-time teledermatopathology. *Dermatol Pract Concept.* 2012;2:3-8.
 58. DeAgustín D, Sanmartín J, Varela-Centelles P, Vidal S, Seoane J. Technological bases for teledermatopathology: state of the art. *Semin Cutan Med Surg.* 2008;27:25-31.
 59. World Health Organization. *Telemedicine: opportunities and developments in Member States: report on the second global survey on eHealth 2009.* Geneva, Switzerland: World Health Organization; 2010
 60. Armstrong AW, Kwong MW, Chase EP, Ledo L, Nesbitt TS, Shewry SL. Why some dermatologists do not practice store-and-forward teledermatology. *Arch Dermatol.* 2012; 148:649-650.
 61. Armstrong A, Kwong MW, Ledo L, Nesbitt TS, Shewry SL. Practice models and challenges in teledermatology: a study of collective experiences from teledermatologists. *PLoS One.* 2011;6:e28687.
 62. Cox NH. A literally blinded trial of palpation in dermatologic diagnosis. *J Am Acad Dermatol.* 2007;56:949-951.
 63. Loane M, Gore H, Corbett R, et al. Preliminary results from the Northern Ireland arms of the UK Multicentre Teledermatology Trial: effect of camera performance on diagnostic accuracy. *J Telemed Telecare.* 1997;3(Suppl 1): 73-75.
 64. Warshaw EM, Lederle FA, Grill JP, et al. Accuracy of teledermatology for pigmented neoplasms. *J Am Acad Dermatol.* 2009;61:753-765.
 65. Aldridge RB, Naysmith L, Ooi ET, Murray CS, Rees JL. The importance of a full clinical examination: assessment of index lesions referred to a skin cancer clinic without a total body skin examination would miss one in three melanomas. *Acta Derm Venereol.* 2013;93:689-692.
 66. Viola KV, Tolpinrud WL, Gross CP, Kirsner RS, Imaeda S, Federman DG. Outcomes of referral to dermatology for suspicious lesions. *Arch Dermatol.* 2011;147:556-560.
 67. Massone C, Hofmann-Wellenhof R, Ahlgren-Siess V, Gabler G, Ebner C, Soyer HP. Melanoma screening with cellular phones. *PLoS One.* 2007;2:e483.
 68. Karavan M, Compton N, Knezevich S, et al. Teledermatology in the diagnosis of melanoma. *J Telemed Telecare.* 2014;20: 18-23.
 69. Ferrandiz L, Ruiz-de-Casas A, Martin-Gutierrez FJ, et al. Effect of teledermatology on the prognosis of patients with cutaneous melanoma. *Arch Dermatol.* 2012;148: 1025-1028.
 70. Viola KV, Federman DG. Effective use of teledermatology: defining expectations and limitations as we move forward. *J Am Acad Dermatol.* 2012;66:157.
 71. Armstrong AW, Dorer DJ, Lugin NE, Kvedar JC. Economic evaluation of interactive teledermatology compared with conventional care. *Telemed J E Health.* 2007; 13:91-99.
 72. Parsi K, Chambers CJ, Armstrong AW. Cost-effectiveness analysis of a patient-centered care model for management of psoriasis. *J Am Acad Dermatol.* 2012;66:563-570.

73. Pak H, Datta S, Triplett C, et al. Cost minimization analysis of a store-and-forward teledermatology consult system. *Telemed J E Health.* 2009;15:160-165.
74. Eminović N, Dijkgraaf MG, Berghout RM, Prins AH, Bindels PJ, de Keizer NF. A cost minimisation analysis in teledermatology: model-based approach. *BMC Health Serv Res.* 2010;10:251.
75. Wootton R, Bloomer S, Corbett R, et al. Multicentre randomised control trial comparing real time teledermatology with conventional outpatient dermatological care: Societal cost-benefit analysis. *BMJ.* 2000;320:1252-1256.
76. Loane M, Oakley A, Rademaker M, Bradfor N, Fleisch P. A cost-minimization analysis of the societal costs of realtime teledermatology compared with conventional care: results from a randomized controlled trial in New Zealand. *J Telemed Telecare.* 2001;7:233-238.
77. Van der Heijden JP, de Keizer NF, Bos JD, Spuls PI, Witkamp L. Teledermatology applied following patient selection by general practitioners in daily practice improves efficiency and quality of care at lower cost. *Br J Dermatol.* 2011;165:1058-1065.
78. Eminovic N, Witkamp L, de Keizer NF, Wyatt JC. Patient perceptions about a novel form of patient-assisted teledermatology. *Arch Dermatol.* 2006;142:647-651.
79. Wood D. Medical connectivity: the move to accountable care organizations includes telemedicine. *Telemed J E Health.* 2011;17:237-240.
80. Moreno-Ramirez D, Ferrandiz L, Ruiz-de-Casas A, et al. Economic evaluation of a store-and-forward teledermatology system for skin cancer patients. *J Telemed Telecare.* 2009;15:40-45.
81. Edison KE, Dyer JA, Whited JD, Mutrux R. Practice gaps. The barriers and the promise of teledermatology. *Arch Dermatol.* 2012;148:650-651.
82. Whited JD. Teledermatology research review. *Int J Dermatol.* 2006;45:220-229.
83. Desai B, McKoy K, Kovarik C. Overview of international teledermatology. *Pan Afr Med J.* 2010;20:1-14.
84. Department of Health and Human Services, Center for Medicare and Medicaid Services website. Medicare Learning Network. Telehealth services. Available at: <http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/telehealthsrvcfcstsh.pdf>. Accessed August 22, 2013.
85. Medicaid website. Telemedicine 2013. Available at: <http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Delivery-Systems/Telemedicine.html>. Accessed August 22, 2013.
86. Porter J, Beierlein J, Burke WA, Phillips CM, Schosser RH. Teledermatology: an examination of per-visit and long-term billing trends at East Carolina University from 1996 to 2007. *J Am Acad Dermatol.* 2010;63:1105-1107.
87. Norum J, Pedersen S, Størmer J, et al. Prioritisation of telemedicine services for large scale implementation in Norway. *J Telemed Telecare.* 2007;13:185-192.
88. Armstrong AW, Sanders C, Farbstein AD, et al. Evaluation and comparison of store-and-forward teledermatology applications. *Telemed J E Health.* 2010;16:424-438.
89. Kaliyadan F. Teledermatology update: mobile teledermatology. *World J Dermatol.* 2013;2:11-15.
90. Afzal RS, Lee RA, Castelo-Soccio L, et al. Reliability and validity of mobile teledermatology in human immunodeficiency virus-positive patients in Botswana: a pilot study. *JAMA Dermatol.* 2014;150:601-607.
91. Berndt RD, Takenga MC, Kuehn S, Preik P, Dubbermann D, Juenger M. Development of a mobile teledermatology system. *Telemed J E Health.* 2012;18:668-673.
92. Brewer AC, Endly DC, Henley J, et al. Mobile applications in dermatology. *JAMA Dermatol.* 2013;149:1300-1304.
93. Wolf JA, Moreau JF, Akilov O, et al. Diagnostic inaccuracy of smartphone applications for melanoma detection. *JAMA Dermatol.* 2013;149:422-426.
94. US Food and Drug Administration website. Jefferson E, Sena A. FDA outlines oversight of mobile medical applications. Available at: <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm263340.htm>. Accessed July 18, 2013.
95. Jesitus J. Teledermatology gains ground, but reimbursement remains a challenge. *Dermatology Times.* Available at: <http://dermatologytimes.modernmedicine.com/dermatology-times/news/modernmedicine/modern-medicine-news/teledermatology-gains-ground-reimbursement2011>. Accessed August 5, 2013.
96. American Academy of Dermatology Association website. AADA position statement on telemedicine. Available at: <http://www.aad.org/forms/policies/Uploads/PS/PS-Telemedicine6-15-07.pdf>. Accessed September 24, 2014.
97. Nelson WA. The ethics of telemedicine. *Healthc Exec.* 2010;25:50-53.
98. Van der Heijden JP, Spuls PI, Voorbraak FP, de Keizer NF, Witkamp L, Bos JD. Tertiary teledermatology: a systematic review. *Telemed J E Health.* 2010;16:56-62.
99. Fleming D, Edison K, Pak H. Telehealth ethics. *Telemed J E Health.* 2009;15:797-803.
100. Weinberg JL, Gormley RH, Kovarik CL. *The computer will see you now: ethics of teledermatology.* Dermatoethics. London: Springer; 2012. pp. 45-49.
101. Scheinfeld N. Photographic images, digital imaging, dermatology, and the law. *Arch Dermatol.* 2004;140:473-476.
102. Rodriguez-Feliz JR, Roth MZ. The mobile technology era: potential benefits and the challenging quest to ensure patient privacy and confidentiality. *Plast Reconstr Surg.* 2012;130:1395-1397.
103. Kluge EW. Ethical and legal challenges for health telematics in a global world: telehealth and the technological imperative. *Int J Med Inform.* 2011;80:e1-e5.
104. Bashshur RL, Shannon GW, Krupinski EA, et al. National telemedicine initiatives: essential to healthcare reform. *Telemed J E Health.* 2009;15:600-610.
105. American Cancer Society website. Cancer facts and figures 2013. Available at: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf>. Accessed September 24, 2014.
106. Rubegni P, Nami N, Cevenini G, et al. Geriatric teledermatology: store-and-forward vs. face-to-face examination. *J Eur Acad Dermatol Venereol.* 2011;25:1334-1339.

Rosacea

Part I. Introduction, categorization, histology, pathogenesis, and risk factors

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Learning objectives

After completing this learning activity, participants should be able to describe the different subtypes of rosacea, including the typical symptoms and phenotypic findings in each of the subtypes; describe in detail the molecular pathogenesis behind rosacea, including the role of microorganisms, the innate immune system, and neuronal dysregulation; and understand the comorbidities most commonly seen in patients with rosacea.

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Rosacea is a chronic inflammatory skin condition that affects approximately 16 million Americans. Four distinct subtypes of rosacea have been recognized, with transient and nontransient facial flushing, telangiectasia, and inflammatory papules and pustules being among the more commonly recognized features. Although the exact pathogenesis of rosacea is unknown, dysregulation of the innate immune system, overgrowth of commensal skin organisms, and aberrant neurovascular signaling may all have a role in promoting the clinical features of rosacea. (J Am Acad Dermatol 2015;72:749-58.)

Key words: cathelicidin; mast cells; matrix metalloproteinases; microbiome; rosacea; serine proteases; transient receptor potential channels; ultraviolet radiation.

ROSACEA CLASSIFICATION

Key points

- Rosacea is typically categorized into 4 main subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular
- Each subtype is distinguished by the presence of certain primary and secondary characteristics

In 2002, the National Rosacea Society Expert Committee developed a classification system for rosacea to help standardize its diagnosis amongst

clinicians and researchers.¹ The committee divided rosacea's diagnostic criteria into primary and secondary characteristics, with the presence of ≥ 1 primary feature being indicative of the diagnosis. Secondary features may or may not be present, and in some cases can occur independently (Table 1). The committee then described 4 rosacea subtypes and 1 variant based on the presence of primary and secondary features. Each subtype is described in detail below. Although the committee agreed that a single patient may present with multiple subtypes simultaneously, whether or not a patient may

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Abbreviations used:

AMP:	antimicrobial peptide
CagA:	cytotoxin-associated gene A
ETR:	erythematotelangiectatic rosacea
IL:	interleukin
KLK5:	kallikrein 5
MMP:	matrix metalloproteinase
PAR2:	protease-activated receptor 2
PPR:	papulopustular rosacea
ROS:	reactive oxygen species
TEWL:	transepidermal water loss
TLR2:	Toll-like receptor 2
TRPA:	transient receptor potential ankyrin
TRPV:	transient receptor potential vanilloid
UV:	ultraviolet

progress from 1 subtype to another remains controversial. Interestingly, a recent paper found that only a small proportion of subjects with erythematotelangiectatic rosacea (ETR) progress to papulopustular rosacea (PPR) or similarly progress from papulopustular rosacea (PPR) to phymatous rosacea.²

Erythematotelangiectatic rosacea (subtype I)

ETR is characterized by nontransient episodes of flushing and persistent central facial erythema¹ (Fig 1, A). Redness may also involve the peripheral face, ears, neck, and upper aspect of the chest, but periocular skin is typically spared.³ Telangiectases are also common in ETR, but they are not required for diagnosis.

Papulopustular rosacea (subtype II)

In addition to the characteristics seen in ETR, patients with PPR experience transient papules or pustules in a central facial distribution¹ (Fig 1, B). In severe cases, these episodes of inflammation can lead to chronic facial edema.⁴

Phymatous rosacea (subtype III)

Phymatous rosacea is characterized by thickened, enlarged skin with irregular surface nodularities¹ (Fig 1, C). These changes can occur in any sebaceous facial region, but the nose is the most commonly affected site. Unlike the other subtypes of rosacea—in which females are predominantly affected—males are more commonly affected by phymatous rosacea.⁵

Ocular rosacea (subtype IV)

Ocular rosacea was defined by the National Rosacea Expert Committee as having ≥ 1 of the following signs or symptoms: watery or bloodshot appearance, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, telangiectases of the conjunctiva and lid margin, or lid and periocular erythema. Other

signs include blepharitis, conjunctivitis, and irregularity of the eyelid margins. Chalazia and styes are also common signs of ocular rosacea.¹ Because there is no diagnostic test for ocular rosacea, the diagnosis relies on the physician's clinical judgment. Ocular involvement is estimated to occur in 6% to 50% of patients with cutaneous rosacea^{6,7} and can occur with or without a diagnosis of cutaneous rosacea.^{7,8} The severity of ocular symptoms may not correlate with the severity of cutaneous findings.^{7,9,10} According to a study of 99 subjects with both ocular and cutaneous rosacea, just more than half of these subjects had cutaneous disease before being diagnosed with ocular rosacea, while 20% of subjects were diagnosed with ocular disease first.¹¹ In rare cases, decreased visual acuity may result from scarring and surface irregularities of the cornea.¹² Therefore, it may be beneficial to screen patients with cutaneous rosacea for ocular symptoms and to consider referring anyone with ocular discomfort or hyperemia of the conjunctiva or lid margin for ophthalmologic evaluation.

HISTOLOGY

Key point

- Skin biopsy findings in rosacea are usually nonspecific and are therefore rarely indicated in the diagnosis of this condition

It is not necessary to obtain a skin biopsy specimen in order to reach a diagnosis of rosacea. Many of the histopathologic findings in the different rosacea subtypes are nonspecific, and therefore obtaining a biopsy specimen should be reserved for cases in which the diagnosis is uncertain or when other diagnoses must be ruled out. In ETR, typical histologic findings include dilation of superficial blood vessels and low-grade perivascular lymphohistiocytic inflammation with occasional plasma cells. In PPR, papules usually contain a prominent perivascular and perifollicular inflammatory infiltrate in the superficial and mid-dermis consisting of lymphocytes, neutrophils, and plasma cells. Pustular lesions usually have a superficial accumulation of neutrophils that, unlike acne vulgaris, extends beyond the follicle.¹³ The histopathologic examination of phymatous rosacea reveals sebaceous gland hyperplasia, follicular plugging, telangiectases, pronounced thickening and fibrosis of the dermis, and large deposits of dermal mucin.¹⁴

PATHOPHYSIOLOGY

The exact pathogenesis of rosacea remains unclear. Although the higher incidence of rosacea

Table I. Diagnostic criteria for rosacea

Presence of ≥ 1 of the following primary features
Flushing (transient erythema)
Nontransient erythema
Papules and pustules
Telangiectases
May include ≥ 1 of the following secondary features
Burning or stinging
Plaque
Dry appearance
Edema
Ocular manifestations
Peripheral location
Phymatous changes

Adapted from Wilkin et al.¹

in individuals of Celtic and Northern European descent suggests that there may be a genetic component to the disorder, genomic association studies have failed to identify a causative gene. Instead, rosacea patients have an increased expression of a variety of genes with roles in both the innate and adaptive immune systems. These results are consistent with findings in the laboratory, where significant research has been dedicated to studying the dysregulation of the innate immune system in rosacea. Microorganisms, such as *Demodex folliculorum*, *Staphylococcus epidermidis*, and others may also contribute to the pathogenesis of rosacea by stimulating the innate immune system. Based on the common triggers for rosacea exacerbations, ultraviolet (UV) light radiation and the transient receptor potential (TRP) family of receptors may also play a role in the pathogenesis of rosacea.

DYSREGULATION OF THE INNATE IMMUNE SYSTEM

Key points

- Rosacea patients have an increased baseline expression of cathelicidin and kallikrein 5, the predominant serine protease responsible for cleaving cathelicidin into its active form
- Increased levels of Toll-like receptor 2, which activates kallikrein 5, are seen in patients with rosacea
- Matrix metalloproteinases that activate kallikrein 5 are also increased in patients with rosacea

Under normal physiologic conditions, triggering the innate immune system leads to controlled increases in cytokines and antimicrobial peptides

(AMPs) in the skin. These normal signaling pathways seem to be disrupted in patients with rosacea. Patients with rosacea have been shown to have increased baseline expression of cathelicidin, an AMP, and kallikrein 5 (KLK5),¹⁵ the predominant serine protease responsible for cleaving cathelicidin into LL-37, its active peptide form^{15,16} (Fig 2). In addition to being more abundant, the forms of KLK5 and LL-37 present in rosacea skin differ from those in normal healthy skin. In rosacea skin, LL-37 is processed into even shorter fragments that have been shown to regulate processes, such as leukocyte chemotaxis, angiogenesis, and expression of extracellular matrix components.^{15,17,18} Injection of these peptide fragments into mouse skin causes a skin response similar to rosacea, strongly supporting their role in the pathogenesis of rosacea.¹⁵

While these findings help explain the final stages in the pathogenesis of rosacea that are responsible for rosacea's clinical manifestations, the underlying trigger for increased cathelicidin and KLK5 production remains unknown. Cathelicidin expression in keratinocytes is strongly induced by vitamin D,¹⁹ which is activated in keratinocytes by UV light, a known trigger of rosacea. Increased levels of TLR2, which play a role in recognizing pathogen-associated molecular patterns, have also been found in lesional skin of patients with rosacea.²⁰ Activation of TLR2 on keratinocytes leads to higher expression and activity levels of KLK5, leading to increased expression of LL-37 and its fragments.¹⁵ Triggers for TLR2 are typically structural molecules on the cell wall of microbes, and although a specific stimulus for TLR2 activation in rosacea patients has not yet been identified, candidates include chitin released from Demodex mites²¹ and lipoproteins from the Demodex-associated Gram-negative bacterium *Bacillus oleronius*.²²

MMPs are another group of molecules that have been shown to indirectly contribute to the activity of KLK5. KLK5 is released as a proenzyme that becomes active after cleavage by MMP-9. The expression of several MMPs, including MMP-2 and MMP-9, are increased in the skin of patients with rosacea.²³ This increased MMP expression in rosacea may activate increased amounts of KLK5, leading to increased LL-37 expression.

Recent work also suggests a possible role for mast cells in the cathelicidin-induced inflammation of rosacea.²⁴ Mast cells have been shown to secrete LL-37 and MMP-9 and trigger the release of inflammatory cytokines,^{20,25} and have also been shown to be upregulated in the skin of patients with rosacea.^{25,26} More recent literature studying the direct role of mast cells in rosacea suggests that these



Fig 1. Rosacea. **A**, Erythematotelangiectatic rosacea is characterized by persistent redness of the central face. Multiple telangiectases are also seen in this patient. **B**, Papulopustular rosacea is characterized by the presence of multiple papules and pustules in addition to facial redness sparing the periocular area. In this patient, the papules and pustules are predominantly located on the malar portion of the face. **C**, Rhinophyma is characterized by hypertrophy of the sebaceous glands, giving the nose an enlarged appearance with an irregular surface.

cells may be responsible for the increased levels of LL-37 and MMP-9.²⁴ Subcutaneous injections of LL-37 into mice lacking mast cells do not cause the classic rosacea features of erythema and telangiectases. Reconstituting the mast cell population in these mice before administering subcutaneous LL-37 causes these features to appear. In addition, these features are not present in wild-type mice, in which mast cell degranulation is first blocked using an intraperitoneal injection of cromolyn sodium, a mast cell stabilizer. These findings suggest that mast cell degranulation may have a role in the increased levels of LL-37 seen in patients with rosacea.

MICROORGANISMS

Key points

- ***Demodex folliculorum* and *Staphylococcus epidermidis* may contribute to rosacea's pathophysiology by stimulating Toll-like receptor 2**
- ***Helicobacter pylori*'s contribution to rosacea symptoms are unclear, but are suggested by the high prevalence of *H pylori* seropositivity in the rosacea population, including a high prevalence of virulent strains of this bacterium**
- ***Bacillus oleronius* exposure may contribute to rosacea's pathophysiology by causing production of matrix metalloproteinase-9, tumor necrosis factor, and interleukin-8**

Microorganisms have been hypothesized to play a role in the pathogenesis of rosacea, but their exact role is unclear. Several studies have reported

differences in the microbial burden of common skin commensals, such as *D folliculorum* and *S epidermidis*, on the skin of healthy subjects and subjects with rosacea, and in bacteria not typically present on the skin, including *Helicobacter pylori* and *Bacillus oleronius*.^{22,27-29} It remains controversial whether this dysbiosis triggers rosacea, or whether the dysbiosis is a response to changes in the skin microenvironment resulting from rosacea's underlying pathophysiology.

The saprophytic mite *D folliculorum* commonly resides in the sebaceous glands of healthy skin. Individuals with rosacea have been shown to have a higher density of Demodex mites on their facial skin compared to individuals without rosacea,³⁰⁻³² suggesting that these mites may play a role in the pathogenesis of rosacea. In 1 study, patients with ETR and PPR had a 5.7-fold increase in *D folliculorum* density compared to healthy controls. Other studies measuring Demodex infestation rates (typically defined as ≥ 5 Demodex mites/cm²) have shown significantly higher infestation rates in rosacea patients, with rates ranging from 35% to 50%.³³⁻³⁶ A study comparing permethrin 5% cream, metronidazole 0.75% gel, and placebo in the treatment of PPR found that permethrin treatment was more effective than metronidazole in terms of decreasing *D folliculorum* colonization, but did not lead to improved clinical efficacy over metronidazole.³⁷ These findings suggest that *D folliculorum* alone is not responsible for rosacea; however, they do not rule out a role for *D folliculorum* in rosacea's pathogenesis.

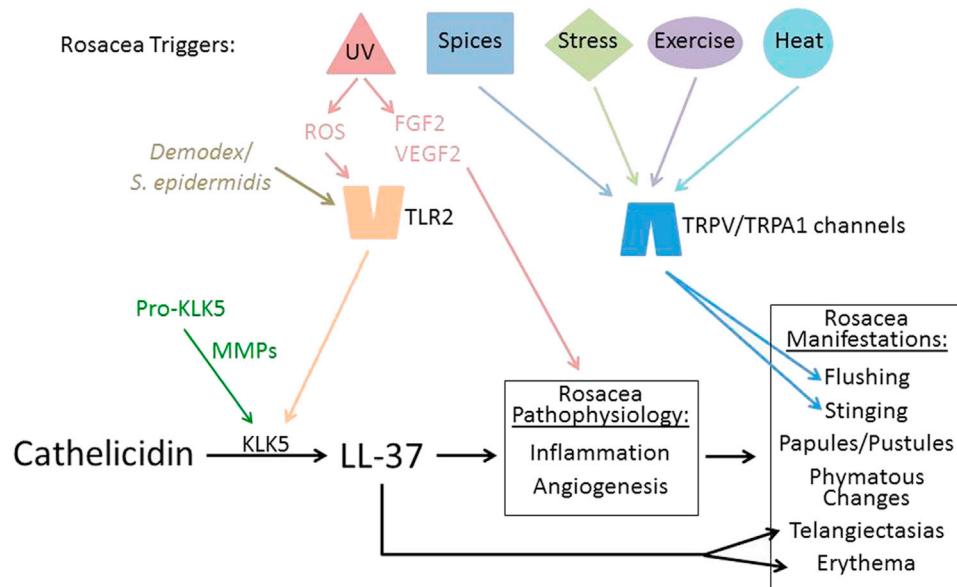


Fig 2. Pathways known to contribute to the pathophysiology and clinical manifestations of rosacea. The cathelicidin gene is cleaved into its active peptide form, LL-37, by kallikrein 5 (KLK5). In patients with rosacea, KLK5 also cleaves cathelicidin into other abnormal peptide fragments. These mutant forms of LL-37 play a role in inflammation and angiogenesis, which contribute to the clinical manifestations seen in rosacea. KLK5 is transformed from a proenzyme to an active enzyme by matrix metalloproteinases. Toll-like receptor 2 signaling, which occurs via activation by such factors as reactive oxygen species or microorganisms, such as *Demodex folliculorum* and *Staphylococcus epidermidis*, can also trigger KLK5 activity, again leading to increased levels of LL-37 and its abnormal peptide fragments. Ultraviolet light radiation, a known trigger of rosacea symptoms for some individuals, can activate ROS, fibroblast growth factor 2, and vascular endothelial growth factor 2, further contributing to the clinical manifestations of rosacea. Other known triggers of rosacea symptoms, including spicy food, stress, exercise, and heat have been shown to activate the transient receptor potential vanilloid receptor, which has been implicated in causing flushing and sensitivity. *FGF2*, Fibroblast growth factor 2; *KLK5*, kallikrein 5; *MMP*, matrix metalloproteinase; *ROS*, reactive oxygen species; *S epidermidis*, *Staphylococcus epidermidis*; *TLR2*, Toll-like receptor 2; *TRPA1*, transient receptor potential ankyrin 1; *TRPV*, transient receptor potential vanilloid receptor; *UV*, ultraviolet light radiation; *VEGF2*, vascular endothelial growth factor 2.

Several studies have proposed mechanisms through which *D folliculorum* may contribute to the pathogenesis of rosacea. Because these mites release chitin, which can activate TLR2,³⁸ the high prevalence of these mites may lead to increased protease activity. In addition, these mites have been shown to harbor the bacterium *B olenorium*, which may also play a role in rosacea's pathogenesis.²²

S epidermidis is the most prevalent commensal bacteria on healthy human skin, where it plays a crucial role in the skin's defense against pathogens. Certain strains of these bacteria produce AMPs shown to selectively inhibit the growth of pathogens, including *Staphylococcus aureus*.³⁹⁻⁴² Cultures of the pustules from PPR patients have shown *S epidermidis* to be the singular bacterium present in these lesions.⁴³ Further investigation of cultured *S*

epidermidis isolates suggests that the strains present on rosacea-affected skin may differ from those present on healthy skin. *S epidermidis* isolates from pustules of PPR patients incubated at 37°C produced different proteins compared to control skin, and these isolates were beta-hemolytic compared to the nonhemolytic properties of *S epidermidis* cultured from control skin.²⁸ These findings suggest that the *S epidermidis* strains present in the skin of patients with rosacea may secrete virulence factors not seen on control skin. These factors may stimulate the innate immune system, leading to the onset or propagation of rosacea symptoms. In addition, *S epidermidis* antigens are recognized by TLR2, and, together with elevated TLR2 levels, increased *S epidermidis* expression in lesional rosacea skin may result in increased expression of AMPs.^{42,44}

The role of *H pylori* and other intestinal bacteria in the pathogenesis of rosacea remains controversial. While some studies report an increased prevalence of *H pylori* seropositivity in patients with rosacea, others have failed to confirm this association.⁴⁵⁻⁴⁷ In addition, findings have varied with respect to whether eradication of these gastrointestinal bacteria improves rosacea.⁴⁶ The fact that oral antibiotics are standard treatment options for both conditions further complicates the interpretation of these findings. Two separate studies separating out patients with previous antibiotic use show a strong correlation between rosacea and *H pylori* infection.^{48,49} Further evidence of the role of *H pylori* in rosacea is supported by the increased number of *H pylori* strains testing positive for the cytotoxin-associated gene A (CagA) protein in patients with rosacea. CagA is an *H pylori* virulence factor. Sixty-seven percent of patients with rosacea tested positive for CagA-positive *H pylori* strains, and 75% were positive for antibodies against CagA.^{50,51} The underlying pathogenesis of how *H pylori* infection triggers rosacea is unknown, though, reinforcing the need for additional studies investigating the relationship between this bacterium and rosacea.

B oleronius is a nonmotile, Gram-negative, endospore-forming bacteria whose role in rosacea was suggested after it was cultured from a *D folliculorum* mite in a patient with rosacea.²² Neutrophils from healthy subjects that have been exposed to *B oleronius* have increased production of MMP-9, tumor necrosis factor, and interleukin-8,⁵² similar to the inflammatory mediators of PPR.^{15,25,53} In rosacea patients, *B oleronius* triggers a proliferative response from a significantly higher number of peripheral blood mononuclear cells than in control subjects,^{22,54,55} again suggesting a role of this bacteria in triggering the symptoms of rosacea.

ULTRAVIOLET LIGHT RADIATION

Key point

- Ultraviolet light radiation increases reactive oxygen species in the skin, which can signal through Toll-like receptor 2 to propagate the kallikrein 5–cathelicidin inflammatory cascade

UV radiation is a known trigger of flushing and can worsen the symptoms of rosacea. The presence of solar elastosis on skin biopsy specimens obtained from patients with rosacea and the high prevalence of rosacea among individuals with fair skin also suggest a role for UV radiation in the pathogenesis of rosacea; however, a recent study examining lifetime UV exposure and prevalence of rosacea failed to

confirm this correlation.⁵⁶ UVA light in particular causes overexpression of MMPs and collagen denaturation,^{57,58} both of which have been shown to contribute either directly or indirectly to the clinical manifestations of rosacea. UVB light increases production and secretion of fibroblast growth factor 2 and vascular endothelial growth factor 2 from human and mouse epidermal keratinocytes,⁵⁹⁻⁶¹ again contributing to the hypervascularity seen in the skin of patients with rosacea. UV radiation also contributes to the majority of ROS present in the skin. Individuals with rosacea have increased levels of ROS in their skin compared to healthy controls.^{53,62} ROS have a proinflammatory effect on the skin, and can signal through TLR2 receptors, further propagating the KLK5–cathelicidin inflammatory cascade present in the skin of patients with rosacea.⁶³ In addition, a recent study suggested that ROS may signal through neurogenic receptors to cause the vasodilator response seen in rosacea.⁶⁴

NEUROGENIC DYSREGULATION

Key points

- Four vanilloid receptors and one ankyrin receptor within the transient receptor potential family of cation channels have been shown to be active in rosacea
- Although signaling pathways of these receptors are not completely understood, these receptors can be activated by stimuli, such as heat and inflammation
- In turn, they may contribute to rosacea symptoms, such as flushing and burning

The fact that many of rosacea's triggers, including temperature changes and spicy food, activate sensory nerves prompted further investigation into the role of the skin's nervous system in rosacea. Two subfamilies within the transient receptor potential (TRP) family of cation channels have emerged as possible contributors to rosacea's pathogenesis based on their functions and their ability to mediate sensory and inflammatory signaling. The first group is the vanilloid (TRPV) receptors, consisting of 6 distinct channels (TRPV1-6), the first 4 of which have been shown to be active in rosacea. The first of these receptors, TRPV1, is expressed by sensory nerves and other nonneuronal cells, such as keratinocytes, where it is activated by capsaicin, heat, and inflammatory states,⁶⁵ and ultimately plays a role in vasoregulation^{66,67} and nociception. TRPV2, -3, and -4 have also been identified on both neuronal and nonneuronal cells, such as keratinocytes, endothelial cells, and immune cells. TRPV2 has a role in innate

immunity, inflammation, nociception, heat sensing, and vascular regulation. TRPV3 and TRPV4 are both activated by increased temperatures; however, TRPV3 is involved in thermosensation and keratinocyte differentiation, while TRPV4 is thought to function as an osmoreceptor and to cause vasodilation and mechanical and inflammation-evoked hyperalgesia. mRNA for TRPV1, -2, and -3 is upregulated in the skin of patients with rosacea compared to healthy control skin, and dermal immunostaining for TRPV2, -3, and -4 was increased in certain rosacea subtypes compared to dermal sections from patients with healthy skin,⁶⁸ further supporting the role of these receptors in rosacea.

The second receptor group consists of the ankyrin (TRPA) channels, with TRPA1 hypothesized to contribute to rosacea's pathogenesis. Like members of the TRPV subfamily of receptors, TRPA1 receptors are located on primary sensory neurons, and in 50% of cases are coexpressed with TRPV1 receptors,⁶⁹ suggesting a possible interaction between them. TRPA1 channels are thermosensitive and can also be activated by spices, such as mustard oil and cinnamaldehyde, the main constituent of cinnamon. In mouse skin, cinnamaldehyde application causes neurogenic vasodilation in a TRPA1-dependent fashion,⁷⁰ supporting the hypothesis that activation of these channels can mediate flushing episodes in rosacea. In addition, recent evidence has also shown that TRPA1 may function as an oxidant sensor for vasodilator responses *in vivo*,⁶⁴ providing yet another mechanism through which ROS may contribute to the pathogenesis of rosacea.

In rat neurons, the TRPA1 channel has been shown to colocalize with protease-activated receptor 2 (PAR2).⁷¹ PAR2 is widely expressed in human skin, where it is activated by proteases, such as trypsin and chymotrypsin, and contributes to the inflammatory response.⁷² Given that the facial skin of patients with rosacea has been shown to have high serine protease activity, it seems possible that PAR2 may be activated by the proteases in rosacea, leading not only to the inflammatory processes seen in rosacea, but also to sensitization of TRPA1, further exacerbating the TRPA1-mediated inflammatory response.⁷³

ABNORMAL BARRIER FUNCTION

Key points

- The skin of patients with rosacea has increased transepidermal water loss and decreased epidermal hydration
- These changes may be related to increased serine protease levels in rosacea and can be reversed with treatment

As a result of the pathophysiologic changes in rosacea, the skin of these patients has been shown to have a decreased barrier function. Compared to control subjects, subjects with both ETR and PPR have increased transepidermal water loss and heightened reactivity to the lactic acid stinging test, a skin irritation test taken to measure skin barrier function.⁷⁴ In another study of subjects with PPR, these patients were found to have reduced epidermal hydration and a more alkaline centrofacial region compared to controls. Treating these patients with a 6-week course of systemic minocycline resulted in decreased erythema and increased epidermal hydration.⁷⁵ One explanation for these changes stems from a study showing that PAR2 activation impedes barrier homeostasis in a serine protease-dependent fashion. In addition, use of a topical serine protease inhibitor in this study accelerated barrier recovery after an acute exacerbation.⁷⁶ These findings suggest that increased serine protease levels in rosacea subjects may contribute to the decreased barrier function and that treating rosacea may help restore the skin barrier.

RISK FACTORS

To date, no specific risk factors have been associated with rosacea. Given that vascular dysregulation has been recognized in the pathophysiology of rosacea, several studies have investigated a potential relationship between rosacea and other conditions in which vascular dysregulation is known to occur. For example, a recent case control study of subjects who suffer from migraines found that women >50 years of age who had migraines had a slightly increased risk of developing rosacea.⁷⁷ Similarly, a case control study of 60 rosacea patients found that these patients had a slightly higher risk of developing cardiovascular disease.⁷⁸ Although it is difficult to draw conclusions from such a limited number of studies, these findings suggest the need for additional investigation into whether the vascular dysfunction seen in rosacea could be signaling a systemic issue.

In conclusion, rosacea is a chronic inflammatory condition affecting skin mainly of the central face. Four main subtypes of rosacea are recognized, all of which are usually diagnosed clinically. Although the cause of rosacea remains unclear, dysregulation of the innate and adaptive immune systems and the nervous system seem to contribute to its pathogenesis, ultimately leading to hypersensitive skin in response to common environmental triggers. Through additional research, advances in the

understanding of rosacea can hopefully shed light on the remaining questions regarding rosacea.

REFERENCES

1. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
2. Tan J, Blume-Peytavi U, Ortonne JP, et al. An observational cross-sectional survey of rosacea: clinical associations and progression between subtypes. *Br J Dermatol*. 2013;169: 555-562.
3. Marks R, Jones EW. Disseminated rosacea. *Br J Dermatol*. 1969;81:16-28.
4. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol*. 2004;51:327-341.
5. Kyriakis KP, Palamaras I, Terzoudi S, Emmanuelides S, Michailides C, Pagana G. Epidemiologic aspects of rosacea. *J Am Acad Dermatol*. 2005;53:918-919.
6. Ramelet AA. Rosacea: a reaction pattern associated with ocular lesions and migraine? *Arch Dermatol* 1994;130:1448.
7. Quarterman MJ, Johnson DW, Abele DC, Lesser JL Jr, Hull DS, Davis LS. Ocular rosacea. Signs, symptoms, and tear studies before and after treatment with doxycycline. *Arch Dermatol*. 1997;133:49-54.
8. Akpek EK, Merchant A, Pinar V, Foster CS. Ocular rosacea: patient characteristics and follow-up. *Ophthalmology*. 1997; 104:1863-1867.
9. Odom R, Dahl M, Dover J, et al. Standard management options for rosacea, part 1: overview and broad spectrum of care. *Cutis*. 2009;84:43-47.
10. Lazaridou E, Fotiadou C, Ziakas NG, Giannopoulou C, Apalla Z, Ioannidis D. Clinical and laboratory study of ocular rosacea in northern Greece. *J Eur Acad Dermatol Venereol*. 2011;25:1428-1431.
11. Ghanem VC, Mehra N, Wong S, Mannis MJ. The prevalence of ocular signs in acne rosacea: comparing patients from ophthalmology and dermatology clinics. *Cornea*. 2003;22: 230-233.
12. Oltz M, Check J. Rosacea and its ocular manifestations. *Optometry*. 2011;82:92-103.
13. Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol*. 1969;100:683-691.
14. Aloia F, Tomasini C, Soro E, Pippione M. The clinicopathologic spectrum of rhinophyma. *J Am Acad Dermatol*. 2000;42: 468-472.
15. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med*. 2007;13:975-980.
16. Yamasaki K, Schaeber J, Coda A, et al. Kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin. *FASEB J*. 2006;20:2068-2080.
17. Koczulla R, von Degenfeld G, Kupatt C, et al. An angiogenic role for the human peptide antibiotic LL-37/hCAP-18. *J Clin Invest*. 2003;111:1665-1672.
18. Morizane S, Yamasaki K, Muhleisen B, et al. Cathelicidin antimicrobial peptide LL-37 in psoriasis enables keratinocyte reactivity against TLR9 ligands. *J Invest Dermatol*. 2012;132: 135-143.
19. Schaeber J, Dorschner RA, Coda AB, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest*. 2007;117: 803-811.
20. Di Nardo A, Vitiello A, Gallo RL. Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. *J Immunol*. 2003;170:2274-2278.
21. Koller B, Muller-Wiefel AS, Rupec R, Korting HC, Ruzicka T. Chitin modulates innate immune responses of keratinocytes. *PLoS One*. 2011;6:e16594.
22. Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol*. 2007;157:474-481.
23. Jang YH, Sim JH, Kang HY, Kim YC, Lee ES. Immunohistochemical expression of matrix metalloproteinases in the granulomatous rosacea compared with the non-granulomatous rosacea. *J Eur Acad Dermatol Venereol*. 2011;25:544-548.
24. Muto Y, Wang Z, Vandenberghe M, Two A, Gallo RL, Di Nardo A. Mast cells are key mediators of cathelicidin initiated skin inflammation in rosacea. *J Invest Dermatol*. 2014;134:2728-2736.
25. Schwab VD, Sulk M, Seeliger S, et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc*. 2011;15:53-62.
26. Aroni K, Tsagroni E, Kavantzas N, Patsouris E, Ioannidis E. A study of the pathogenesis of rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. *Arch Dermatol Res*. 2008;300:125-131.
27. Forton F, Seys B, Marchal JL, Song AM. *Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy. *Br J Dermatol*. 1998;138: 461-466.
28. Dahl MV, Ross AJ, Schlievert PM. Temperature regulates bacterial protein production: possible role in rosacea. *J Am Acad Dermatol*. 2004;50:266-272.
29. Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol*. 1994;89: 1603-1604.
30. Lacey N, Kavanagh K, Tseng SC. Under the lash: Demodex mites in human diseases. *Biochem (London)*. 2009;31:2-6.
31. Jarmuda S, O'Reilly N, Zaba R, Jakubowicz O, Szkaradkiewicz A, Kavanagh K. Potential role of Demodex mites and bacteria in the induction of rosacea. *J Med Microbiol*. 2012;61:1504-1510.
32. Zhao YE, Wu LP, Peng Y, Cheng H. Retrospective analysis of the association between Demodex infestation and rosacea. *Arch Dermatol*. 2010;146:896-902.
33. Casas C, Paul C, Lahfa M, et al. Quantification of *Demodex folliculorum* by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol*. 2012;21: 906-910.
34. Moravvej H, Dehghan-Mangabadi M, Abbasian MR, Meshkat-Razavi G. Association of rosacea with demodicosis. *Arch Iran Med*. 2007;10:199-203.
35. Roihu T, Kariniemi AL. Demodex mites in acne rosacea. *J Cutan Pathol*. 1998;25:550-552.
36. Bonamigo RR, Bakos L, Edelweiss M, Cartell A. Could matrix metalloproteinase-9 be a link between *Demodex folliculorum* and rosacea? *J Eur Acad Dermatol Venereol* 2005;19:646-647.
37. Kocak M, Yagli S, Vahapoglu G, Eksioglu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. *Dermatology*. 2002; 205:265-270.
38. Ferrer L, Favera I, Silbermayr K. Immunology and pathogenesis of canine demodicosis. *Vet Dermatol*. 2014;25:427-e65.

39. Bastos MC, Ceotto H, Coelho ML, Nascimento JS. Staphylococcal antimicrobial peptides: relevant properties and potential biotechnological applications. *Curr Pharm Biotechnol.* 2009;10:38-61.
40. Cogen AL, Yamasaki K, Muto J, et al. *Staphylococcus epidermidis* antimicrobial delta-toxin (phenol-soluble modulin-gamma) cooperates with host antimicrobial peptides to kill group A *Streptococcus*. *PloS One.* 2010;5:e8557.
41. Cogen AL, Yamasaki K, Sanchez KM, et al. Selective antimicrobial action is provided by phenol-soluble modulins derived from *Staphylococcus epidermidis*, a normal resident of the skin. *J Invest Dermatol.* 2010;130:192-200.
42. Gallo RL, Nakatsuji T. Microbial symbiosis with the innate immune defense system of the skin. *J Invest Dermatol.* 2011;131:1974-1980.
43. Whitfeld M, Gunasingam N, Leow LJ, Shirato K, Preda V. *Staphylococcus epidermidis*: a possible role in the pustules of rosacea. *J Am Acad Dermatol.* 2011;64:49-52.
44. Wanke I, Steffen H, Christ C, et al. Skin commensals amplify the innate immune response to pathogens by activation of distinct signaling pathways. *J Invest Dermatol.* 2011;131:382-390.
45. Lazaridou E, Giannopoulou C, Fotiadou C, Vakirlis E, Trigoni A, Ioannides D. The potential role of microorganisms in the development of rosacea. *J Dtsch Dermatol Ges.* 2011;9:21-25.
46. Tuzun Y, Keskin S, Kote E. The role of *Helicobacter pylori* infection in skin diseases: facts and controversies. *Clin Dermatol.* 2010;28:478-482.
47. Mc Aleer MA, Lacey N, Powell FC. The pathophysiology of rosacea. *G Ital Dermatol Venereol.* 2009;144:663-671.
48. Lazaridou E, Apalla Z, Sotiraki S, Ziakas NG, Fotiadou C, Ioannides D. Clinical and laboratory study of rosacea in northern Greece. *J Eur Acad Dermatol Venereol.* 2010;24:410-414.
49. Bonamigo RR, Leite CS, Wagner M, Bakos L. Rosacea and *Helicobacter pylori*: interference of systemic antibiotic in the study of possible association. *J Eur Acad Dermatol Venereol.* 2000;14:424-425.
50. Szlachcic A. The link between *Helicobacter pylori* infection and rosacea. *J Eur Acad Dermatol Venereol.* 2002;16:328-333.
51. Argenziano G, Donnarumma G, Iovene MR, Arnone P, Baldassarre MA, Baroni A. Incidence of anti-*Helicobacter pylori* and anti-CagA antibodies in rosacea patients. *Int J Dermatol.* 2003;42:601-604.
52. O'Reilly N, Bergin D, Reeves EP, McElvaney NG, Kavanagh K. Demodex-associated bacterial proteins induce neutrophil activation. *Br J Dermatol.* 2012;166:753-760.
53. Bakar O, Demircay Z, Yuksel M, Haklar G, Sanisoglu Y. The effect of azithromycin on reactive oxygen species in rosacea. *Clin Exp Dermatol.* 2007;32:197-200.
54. Li J, O'Reilly N, Sheha H, et al. Correlation between ocular Demodex infestation and serum immunoreactivity to bacillus proteins in patients with facial rosacea. *Ophthalmology.* 2010;117:870-877.e1.
55. O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated bacillus proteins and erythematotelangiectatic rosacea. *Br J Dermatol.* 2012;167:1032-1036.
56. McAleer MA, Fitzpatrick P, Powell FC. Papulopustular rosacea: prevalence and relationship to photodamage. *J Am Acad Dermatol.* 2010;63:33-39.
57. Naru E, Suzuki T, Moriyama M, et al. Functional changes induced by chronic UVA irradiation to cultured human dermal fibroblasts. *Br J Dermatol.* 2005;153(suppl 2):6-12.
58. Kawaguchi Y, Tanaka H, Okada T, et al. The effects of ultraviolet A and reactive oxygen species on the mRNA expression of 72-kDa type IV collagenase and its tissue inhibitor in cultured human dermal fibroblasts. *Arch Dermatol Res.* 1996;288:39-44.
59. Brauchle M, Funk JO, Kind P, Werner S. Ultraviolet B and H₂O₂ are potent inducers of vascular endothelial growth factor expression in cultured keratinocytes. *J Biol Chem.* 1996;271:21793-21797.
60. Ballaun C, Weninger W, Uthman A, Weich H, Tschachler E. Human keratinocytes express the three major splice forms of vascular endothelial growth factor. *J Invest Dermatol.* 1995;104:7-10.
61. Bielenberg DR, Bucana CD, Sanchez R, Donawho CK, Kripke ML, Fidler IJ. Molecular regulation of UVB-induced cutaneous angiogenesis. *J Invest Dermatol.* 1998;111:864-872.
62. Jones D. Reactive oxygen species and rosacea. *Cutis.* 2004;74:17-20, 32-4.
63. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci.* 2009;55:77-81.
64. Graepel R, Fernandes ES, Aubdool AA, Andersson DA, Bevan S, Brain SD. 4-oxo-2-nonenal (4-ONE): evidence of transient receptor potential ankyrin 1-dependent and -independent nociceptive and vasoactive responses in vivo. *J Pharmacol Exp Ther.* 2011;337:117-124.
65. Pecze L, Szabo K, Szell M, et al. Human keratinocytes are vanilloid resistant. *PloS One.* 2008;3:e3419.
66. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature.* 1997;389:816-824.
67. Earley S. Vanilloid and melastatin transient receptor potential channels in vascular smooth muscle. *Microcirculation.* 2010;17:237-249.
68. Sulk M, Seeliger S, Aubert J, et al. Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. *J Invest Dermatol.* 2012;132:1253-1262.
69. Andersson DA, Gentry C, Alenmyr L, et al. TRPA1 mediates spinal antinociception induced by acetaminophen and the cannabinoid delta(9)-tetrahydrocannabinol. *Nat Commun.* 2011;2:551.
70. Pozsgai G, Bodkin JV, Graepel R, Bevan S, Andersson DA, Brain SD. Evidence for the pathophysiological relevance of TRPA1 receptors in the cardiovascular system in vivo. *Cardiovasc Res.* 2010;87:760-768.
71. Dai Y, Wang S, Tominaga M, et al. Sensitization of TRPA1 by PAR2 contributes to the sensation of inflammatory pain. *J Clin Invest.* 2007;117:1979-1987.
72. Steinhoff M, Buddenkotte J, Shpacovitch V, et al. Proteinase-activated receptors: transducers of proteinase-mediated signaling in inflammation and immune response. *Endocr Rev.* 2005;26:1-43.
73. Aubdool AA, Brain SD. Neurovascular aspects of skin neurogenic inflammation. *J Investig Dermatol Symp Proc.* 2011;15:33-39.
74. Dirschka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br J Dermatol.* 2004;150:1136-1141.
75. Ni Raghallaigh S, Powell FC. Epidermal hydration levels in rosacea patients improve after minocycline therapy. *Br J Dermatol.* 2014;171:259-266.
76. Hachem JP, Houben E, Crumrine D, et al. Serine protease signaling of epidermal permeability barrier homeostasis. *J Invest Dermatol.* 2006;126:2074-2086.

77. Spoendlin J, Voegel JJ, Jick SS, Meier CR. Risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs. *J Invest Dermatol.* 2013;133:2790-2793.
78. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. *J Eur Acad Dermatol Venereol.* 2014;28:1165-1169.

Rosacea

Part II. Topical and systemic therapies in the treatment of rosacea

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Learning objectives

After completing this learning activity, participants should be able to develop a treatment plan for rosacea using a symptom-based approach; describe the efficacy, safety, and mechanism of action of current rosacea therapies; and identify emerging rosacea treatments.

Disclosures

Editors

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Although rosacea's impact on physical health is limited, it has profound effects on a person's psychological well-being. Therefore, treating rosacea can greatly affect a person's quality of life. Patient education regarding trigger avoidance and skin care techniques such as moisturizing and sun protection are important non-pharmacologic first steps in treating rosacea. Pharmacologic interventions range from topical to systemic medications, with the ideal medication choice dependent on the symptoms and severity of each individual patient. Despite this variety of therapeutic options, none of these therapies are completely curative, and therefore further research into the pathophysiology of rosacea is required in order to create more targeted and efficacious treatment options. (J Am Acad Dermatol 2015;72:761-70.)

Key words: alpha-adrenergic receptor agonists; azelaic acid; isotretinoin; metronidazole; rosacea; tetracyclines.

TREATMENT OF ROSACEA

Key point

- **Rosacea treatments focus on 3 main categories: patient education, skin care, and pharmacologic/procedural interventions**

Rosacea is a chronic inflammatory skin condition that affects the central portion of the face. Although rosacea itself is a relatively benign condition, there are significant morbidities associated with rosacea in

Abbreviations used:

ETR:	erythematotelangiectatic rosacea
FDA:	US Food and Drug Administration
KLK5:	kallikrein 5
MMP:	matrix metalloproteinase
PPR:	papulopustular rosacea
ROS:	reactive oxygen species
TLR2:	Toll-like receptor 2
UV:	ultraviolet

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terms of its impact on patients' quality of life and psychological well-being.¹ For example, one study found that 75% of affected individuals experience low self-esteem, and that the odds for being diagnosed with depressive disorder in the rosacea patient population is 4.81 compared to that of the general population.² These findings highlight the necessity of controlling the symptoms of rosacea. A variety of both topical and systemic treatment options are available for these patients, however, patient education and routine skin care are also important aspects of treating rosacea. All of these aspects of rosacea management will be discussed below.

PATIENT EDUCATION

Taking a thorough history and spending quality time reassuring patients of the benign nature of their skin condition are beneficial to the psychological well-being of patients. If specific triggers or exacerbating factors can be identified, avoiding these triggers, if possible, can be beneficial in controlling an individual's symptoms. Common triggers include wind, hot and cold temperatures, exercise, spicy foods, alcohol, hot drinks, and physical or psychological stress.³ Medication reconciliation also plays an important role in the treatment of rosacea, because common medications, such as niacin or the application of topical steroids to the face, can exacerbate flushing.^{4,5} Finally, personally addressing the most bothersome aspects of each individual's disease process and discussing realistic goals of therapy can improve patient–physician communication and patients' quality of life.

SKIN CARE/NONPHARMACOLOGIC TREATMENTS

Key points

- Moisturizers are an important aspect of treating rosacea because rosacea skin has increased transepidermal water loss
- By blocking ultraviolet light, sunscreens decrease LL-37 production and the subsequent production of reactive oxygen species that can trigger rosacea

Proper skin care plays a pivotal role in maintaining remission and alleviating the symptoms of rosacea. Rosacea skin has been shown to have increased transepidermal water loss indicative of defective barrier functions, and therefore moisturizers are important to help restore this barrier and facilitate remission of rosacea exacerbations.⁶ A study comparing the effects of using metronidazole

0.75% gel plus a gentle nonirritating moisturizing cream (Cetaphil; Galderma, Uppsala, Sweden) to metronidazole alone found that patients applying metronidazole 0.75% gel plus the moisturizer reported improved skin dryness, roughness, desquamation, and skin sensitivity compared to patients applying metronidazole alone.⁷ Therefore, diligent skin care, including mild cleansing, moisturizing, and sun protection has been shown to significantly improve skin hydration, objective and subjective skin sensitivity, and overall skin health.⁸

Acute ultraviolet (UV) light exposure is known to trigger rosacea symptoms because it stimulates LL-37 production and has been suggested to deplete antioxidant reserves in the skin^{9–12} and increase the production of reactive oxygen species (ROS).^{13–15} Therefore, daily sun protection is an essential part of skin care and maintenance in patients with rosacea.^{16–18} Many topical sun blocks can be irritating to rosacea patients, so choosing a well-tolerated regimen can be difficult.³ While no specific sunscreen products have been shown to be consistently most beneficial in patients with rosacea, a product with a sun protectant factor of at least 30 should be recommended to rosacea patients.¹⁸ Finding the most convenient and tolerable skin care regimen for these patients is crucial to improving symptoms and preventing relapse.

PHARMACOLOGIC TREATMENTS

Topical medications

Key points

- Topical treatments approved by the US Food and Drug Administration for rosacea include topical sodium sulfacetamide, azelaic acid, metronidazole, and the alpha-adrenergic agonist brimonidine
- The off-label use of topical retinoids, topical calcineurin inhibitors, topical macrolides, benzoyl peroxide, topical permethrin cream, and ivermectin cream have also shown to be somewhat beneficial in treating rosacea in smaller case series

Topical sodium sulfacetamide

- Topical sodium sulfacetamide is useful in treating patients with rosacea, especially those who have concomitant seborrheic dermatitis.

Topical sodium sulfacetamide/sulfur formulations are now available in several vehicles that have been approved by the US Food and Drug Administration (FDA), including lotions, creams, and cleansers. The

most common formulation consists of 10% sodium sulfacetamide with 5% sulfur lotion, applied twice daily. Efficacy of the lotion has been reported in papulopustular rosacea (PPR) in multiple studies.^{19,20} One controlled, double-blind study of 103 patients noted a 65% decrease in inflammatory lesions and a 66% decrease in facial erythema compared to 44% and 33% reductions, respectively, in the control group.²¹ Sulfacetamide cleansers have also shown repeated efficacy when used in combination with other products, such as topical metronidazole.²⁰ Although the exact mechanism of sodium sulfacetamide is unknown, it is thought to have antiinflammatory effects based on clinical studies and clinical experience.^{19,20} The most common adverse reactions include dryness, erythema, or irritation at the application site, which decrease in frequency over time.²¹ Topical sulfacetamide is also particularly useful in treating patients with rosacea with concomitant seborrheic dermatitis, which can be fairly common.²⁰

Topical metronidazole

- **Topical metronidazole is thought to be beneficial in rosacea because of its ability to decrease reactive oxygen species generation and inactivate existing reactive oxygen species production.**

Topical metronidazole has been used as a topical treatment for rosacea since the 1950s. The clinical efficacy of metronidazole has been attributed to its ability to decrease ROS generation and inactivate existing ROS production (Fig 1).¹⁴ Compared to placebo, metronidazole has been shown to be more efficacious in reducing erythema, papules, and pustules in multiple trials of patients with moderate to severe rosacea.²²⁻²⁶ Metronidazole cream is available in 2 concentrations: 0.75% and 1%. Both creams have proven equally efficacious at reducing erythema, papules, and pustules when applied once daily.²⁷ Metronidazole has also been shown to maintain remission after discontinuation of treatment. Compared to 42% of subjects in the tetracycline group, only 23% of subjects in the metronidazole group had a relapse of their symptoms 6 months after discontinuation of their assigned therapy.²⁸⁻³⁰

Topical azelaic acid

- **Azelaic acid has been shown to decrease expression of kallikrein 5 and cathelicidin.**

Azelaic acid, a naturally occurring saturated dicarboxylic acid, is available as a 15% azelaic acid gel and 20% azelaic acid cream for the treatment of rosacea, and both have been approved for use by the

FDA. These formulations have been shown to improve rosacea symptoms.^{31,32} According to a 2011 Cochrane review, pooled participant-assessed data from 6 studies showed that 70% to 80% of patients using azelaic acid reported complete remission or marked improvement in their rosacea symptoms, compared to only a 50% to 55% response rate reported by the placebo group.²² Although previous studies have suggested that the mechanism of action of azelaic acid in treating rosacea is via its anti-inflammatory properties and ability to decrease ROS,³³ a recent study on 55 adults with papulopustular rosacea found that twice daily application of 15% azelaic acid gel decreases expression of both kallikrein 5 (KLK5) and cathelicidin, suggesting that this medication directly targets the increased KLK5 and cathelicidin levels thought to contribute to rosacea's pathogenesis (Fig 1).³⁴ Azelaic acid is generally well tolerated and serves as a viable treatment option for rosacea patients.

Topical alpha-adrenergic receptor agonists

- **Topical alpha-adrenergic receptor agonists have been shown to reduce persistent facial erythema in rosacea by vasoconstricting dermal blood vessels.**
- **Brimonidine tartrate 0.5% is approved by the US Food and Drug Administration for the treatment of rosacea-associated erythema.**
- **Oxymetazoline has also been shown to significantly reduce baseline erythema in patients with rosacea and is currently undergoing phase III clinical trials.**

Topical alpha-adrenergic receptor agonists have recently been recognized as a treatment for the persistent facial erythema seen in rosacea. These agents work specifically on the smooth muscles surrounding the vessels of the superficial and deep dermal plexuses. Upon binding to receptors on these muscles, these medications cause vasoconstriction (Fig 1),³⁵ diverting blood flow away from the central face and reducing the persistent centrofacial erythema seen in rosacea. These agents do not impact telangiectasias, though, because these vessels lack vasomotor tone; nor do they affect inflammatory lesions, making them uniquely suited for the treatment of persistent erythema alone.

The alpha-2 agonist brimonidine tartrate gel 0.5% (brimonidine gel 0.33%) was recently approved by the FDA for once-daily application for treating rosacea-associated erythema. Clinical trials have shown a reduction in baseline facial erythema in as few as 30 minutes after application of the gel, with maximal erythema reduction lasting between 6 and 7 hours after a single application.^{36,37} After this time,

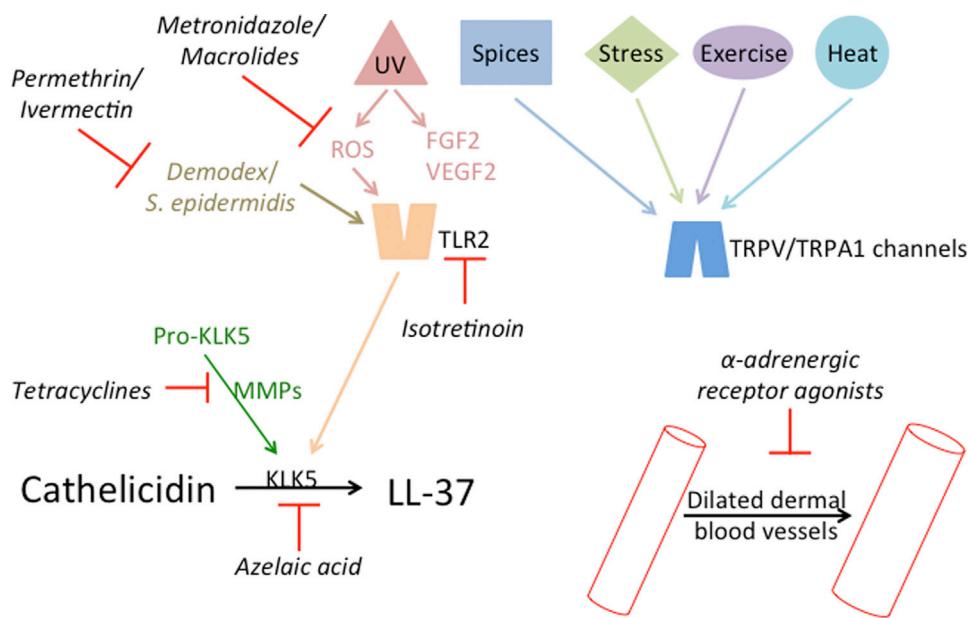


Fig 1. Mechanism of action of rosacea treatments. Metronidazole and macrolides inhibit reactive oxygen species production. Ivermectin and permethrin are antiparasitic agents used to treat cutaneous demodicidosis. Isotretinoin inhibits Toll-like receptor 2 signaling. Azelaic acid decreases kallikrein 5 and cathelicidin expression. Tetracyclines inhibit matrix metalloproteinases.

the patient's erythema scores returned to baseline, with <5% of subjects noting an adverse response of rebound or a sudden return of erythema. In a separate study of the posttreatment effects of brimonidine tartrate gel 0.5%, erythema scores 28 days after discontinuation of the drug were either the same or reduced compared to baseline scores, and these scores differed significantly compared to placebo. In addition, rebound facial erythema was not noted at this time point.³⁶ Overall, bromonidine appears to be well tolerated and have a favorable safety profile, despite scattered reports of rebound erythema have been reported in the literature. In all cases thus far, the rebound erythema has been reversible, but patients should be advised of this possibility before beginning to take this medication.^{38,39}

Oxymetazoline, a selective alpha-1 adrenergic receptor agonist, has also been used to treat rosacea. In 2 adult subjects with erythematotelangiectatic rosacea (ETR), once daily application of oxymetazoline 0.05% led to a decrease in rosacea-associated redness when applied to the affected skin.⁴⁰ These effects were observed within 1 to 3 hours of application and lasted for several hours in both patients. Oxymetazoline 0.05% is currently undergoing phase III trials to evaluate its efficacy in rosacea.

In subjects presenting with persistent facial erythema and inflammatory lesions, alpha-adrenergic agonists

can be used in combination with antiinflammatory agents, such as metronidazole, azelaic acid, and oral antibiotics, to better target specific disease manifestations in individual patients.

Topical medications for rosacea that have not been approved by the US Food and Drug Administration

The off-label use of topical retinoids, topical calcineurin inhibitors (TCIs), benzoyl peroxide, topical permethrin cream, and ivermectin cream have also proven to be somewhat beneficial in treating rosacea in smaller case series (Table I). Of these, topical retinoids, TCIs, topical permethrin cream, and topical ivermectin cream will be discussed in additional detail below.

Topical retinoids

- **Topical retinoids promote connective tissue remodeling and downregulate Toll-like receptor 2 expression.**

Topical retinoids have been shown to repair photodamaged skin by promoting connective tissue remodeling.^{41,42} Therefore, it has been theorized that topical retinoids may be effective in decreasing rosacea symptoms by reversing the contribution of UV radiation to rosacea's manifestations.⁴³ In addition, tretinoin, an all trans retinoic acid, has been shown to down-regulate Toll-like receptor 2 (TLR2) expression in human monocytes in vitro.⁴⁴

Table I. Topical medications shown to be beneficial in the treatment of rosacea*

Medication name	Level of evidence	Mechanism of action
Treatments approved by the FDA		
Sodium sulfacetamide	IA	Unknown, but likely antiinflammatory ^{19,20}
Metronidazole	IA	Decreased ROS generation and inactivates existing ROS production ¹⁴
Azelaic acid	IA	Decreased expression of KLK5 and cathelicidin ³⁴
Alfa-adrenergic agonists	IB	Vasoconstriction of smooth muscles surrounding vessels of the superficial and deep dermal plexuses ³⁵
Treatments not approved by the FDA		
Retinoids	IIB	Connective tissue remodeling ^{39,40} and TLR2 downregulation ⁴⁴
Calcineurin inhibitors	IIB	Antiinflammatory ^{51,52}
Benzoyl peroxide	IB	Unknown
Permethrin	IB	Antiparasitic properties treat cutaneous demodicidosis ^{53,54}
Ivermectin [†]	IB	Antiparasitic properties treat cutaneous demodicidosis ⁵³

Level of evidence: IA evidence includes evidence from metaanalysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

FDA, US Food and Drug Administration; *KLK5*, kallikrein 5; *ROS*, reactive oxygen species; *TLR2*, Toll-like receptor 2.

*This table lists topical medications shown to improve rosacea that have been approved by the FDA, those that have not been approved by the FDA, the level of evidence supporting the use of each treatment, and the mechanism of action of each treatment.

[†]Ivermectin has now received FDA approval.

Therapy with tretinoin may therefore be beneficial because of its downregulation of TLR2 expression. Topical tretinoin as a monotherapy or in combination with other topical agents has been reported in multiple studies to clinically reduce erythema, papules and pustules, and telangiectasias.^{45,46} One study compared treatments of either oral or topical retinoid or both among 20 rosacea subjects. The results found that while oral isotretinoin produced more rapid improvement, all subjects had significant reductions in papules, pustules, and erythema.⁴⁵ However, the study was not well controlled, because placebo cream was only used in the final 16 weeks while retinoid treatments were withheld. More data are therefore needed to show the clinical efficacy of topical retinoids.²²

Topical calcineurin inhibitors

- **Topical calcineurin inhibitors are hypothesized to be beneficial in reducing rosacea symptoms because of their ability to inhibit T-cell activation, thereby preventing the release of proinflammatory cytokines.**

The TCIs pimecrolimus and tacrolimus have both been used to treat ETR and PPR. Studies measuring their efficacy in improving rosacea symptoms have had mixed results. Both medications have led to significant improvement in erythema in separate open-label studies^{47,48}; however, 2 randomized controlled trials comparing

pimecrolimus cream 1% to vehicle found no significant difference in erythema between the 2 groups at week 4.^{49,50} TCIs are antiinflammatory in nature, and their role in rosacea likely relates to their ability to inhibit T cell activation, thereby preventing the release of inflammatory cytokines from both T cells and mast cells.^{51,52} Additional studies of these medications in the rosacea population may help better define the role of these agents in this condition.

Topical permethrin cream. Permethrin cream 5% has been tested in the rosacea population based on its ability to treat cutaneous demodicidosis (Fig 1).^{53,54} In a randomized, double blind study comparing permethrin to metronidazole gel 0.75%, these 2 medications had equal efficacy in terms of reducing erythema and papules.⁵⁵ Subjects randomized to the permethrin group did not have changes with respect to telangiectasias, rhinophyma, or pustule counts. This therapy can therefore be considered in subjects with specific complaints of erythema or papules.

Ivermectin cream. Ivermectin cream is currently undergoing investigation as a possible rosacea treatment. Oral ivermectin has been recognized as a treatment for cutaneous demodicidosis,⁵³ which has been postulated to play a role in the pathophysiology of rosacea (Fig 1). Whether a cream formulation of ivermectin can produce the same result is currently being studied. Several phase III clinical trials are currently underway on this topic.

Table II. Systemic medications shown to be beneficial in the treatment of rosacea*

Medication name	Level of evidence	Mechanism of action
Treatments approved by the FDA		
Tetracyclines	IA	Antiinflammatory; decrease KLK5 activity by inhibiting MMPs ⁶¹
Treatments not approved by the FDA		
Beta-adrenergic receptor antagonists	III	Vasoconstriction of smooth muscles surrounding blood vessels ⁶⁵
Isotretinoin	IB	Downregulation of TLR2 ⁷³

Level of evidence: IA evidence includes evidence from metaanalysis of randomized controlled trials; IB evidence includes evidence from at least 1 randomized controlled trial; IIA evidence includes evidence from at least 1 controlled study without randomization; IIB evidence includes evidence from at least 1 other type of experimental study; III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

FDA, US Food and Drug Administration; *KLK5*, kallikrein 5; *MMP*, matrix metalloproteinase; *TLR2*, Toll-like receptor 2.

*This table lists systemic medications shown to improve rosacea that have been approved by the FDA, those that have not been approved by the FDA, the level of evidence supporting the use of each treatment, and the mechanism of action of each treatment.

(clinicaltrial.gov identifiers NCT01493687, NCT01494467, and NCT01493947).*

SYSTEMIC MEDICATIONS

Key points

- **Tetracyclines have been the foundation of systemic rosacea therapy for >50 years**
- **Beta-blockers and isotretinoin have also been shown to have therapeutic benefits in rosacea; however, these medications are not approved by the US Food and Drug Administration for use in patients with rosacea**

Tetracyclines

Key point

- **Antiinflammatory dosing of doxycycline improves the manifestations of rosacea by decreasing matrix metalloproteinase expression, downregulating inflammatory cytokines, reducing reactive oxygen species levels, and inhibiting nitric oxide-mediated vasodilation**

Although tetracyclines have been used to treat rosacea for >50 years, FDA approval for the first systemic medication for treating PPR came in 2006 with the approval of doxycycline at antiinflammatory doses. Before its approval, doxycycline at both antimicrobial (50–200 mg daily) and antiinflammatory (<50 mg daily) doses, and less commonly tetracycline, were the most frequently prescribed agents for PPR. While antimicrobial dosing of doxycycline has been shown to reduce inflammatory lesion counts in PPR, its necessity was questioned because no definite bacterial pathogen has been identified in rosacea.^{56,57} Since then,

multiple studies have shown the clinical efficacy of antiinflammatory dose doxycycline in improving the symptoms of PPR.^{58–60} Antiinflammatory dosing of doxycycline has been shown to decrease expression of matrix metalloproteinases (MMPs) that proteolytically cleave the serine protease KLK5 into its active form⁶¹ (Table II and Fig 1). In addition, low-dose doxycycline in rosacea has been shown to downregulate inflammatory cytokines that contribute to neutrophil infiltration, reduce levels of ROS that destroy connective tissue, and inhibit nitric oxide to reduce vasodilation.⁶² It has been proposed that the antiinflammatory effects of tetracyclines are the main mechanism of action in reducing rosacea symptoms,^{63,64} suggesting that the antibacterial properties of doxycycline have a limited role in rosacea at best.

Beta-blockers

Key point

- **By vasoconstricting dermal blood vessels, beta-blockers have been shown to decrease erythema and flushing in some rosacea patients**

Several case reports have suggested a role for beta-blockers in the treatment of rosacea. In 2005, a case series of 9 patients with rosacea reported that 8 patients had fewer instances of and less severe flushing with propranolol.⁶⁵ Later reports on carvedilol have shown dramatic decreases in facial redness 2 to 3 weeks after treatment initiation in ETR patients with facial redness refractory to multiple other agents.^{66,67} Although the patients in these reports tolerated these medications well, hypotension and bradycardia are always a concern when administering these medications to normotensive subjects.⁶⁷

*Author addendum: Since the acceptance of this article, ivermectin cream has received FDA approval.

Nonselective beta-blockers are thought to decrease erythema and flushing in rosacea by inhibiting beta-adrenergic receptors on the smooth muscles surrounding blood vessels, leading to vasoconstriction of these vessels.⁶⁵ These medications may also reduce anxiety and tachycardia, both of which can exacerbate flushing episodes.⁶⁷ Carvedilol has also been shown to have antioxidant and antiinflammatory actions, which may further contribute to its efficacy in rosacea.⁶⁶

Isotretinoin

Key point

- **Isotretinoin may be useful in treating patients with severe, recalcitrant papulopustular rosacea by downregulating Toll-like receptor 2 expression**

Although it has not been approved by the FDA for the treatment of rosacea, several studies have shown that oral isotretinoin is an effective treatment for severe, recalcitrant PPR.^{3,68,69} The reported dose for recalcitrant rosacea ranges from 0.5 to 1.0 mg/kg daily; however, studies have also shown that low-dose isotretinoin (10 mg daily) is effective in treating refractory rosacea with evidence of less adverse effects.^{69,70} In another study, the efficacy of lower doses of isotretinoin (0.1, 0.3, or 0.5 mg/kg per day) was compared to doxycycline and placebo among 573 patients.⁷¹ After 12 weeks, isotretinoin 0.3 mg/kg proved to be the most effective daily dose. When compared to doxycycline, this dose of isotretinoin had superior efficacy, with subjects having a 90% reduction in inflammatory lesions compared to the 83% reduction seen with doxycycline. The safety profile of isotretinoin in these subjects was similar to that seen in the treatment of acne, and therefore routine safety and laboratory monitoring is required.⁷¹

Although in vitro 13-cis retinoic acid (isotretinoin) has been shown to induce KLK5 and KLK7 expression in cultured keratinocytes,⁷² in vivo isotretinoin has been shown to significantly decrease monocyte TLR-2 expression.⁷³ The effectiveness of isotretinoin in the treatment of rosacea is therefore thought to be secondary to the downregulation of TLR2 (Fig 1).⁷³

CONSENSUS RECOMMENDATIONS FROM THE AMERICAN ACNE AND ROSACEA SOCIETY

In 2014, the American Acne and Rosacea Society published consensus recommendations on the management of rosacea.⁷⁴ In these recommendations,

rosacea is divided into 2 major common types: (1) centrofacial erythema with papulopustular lesions and (2) centrofacial erythema without papulopustular lesions. Centrofacial erythema with papulopustular lesions is then further classified as mild (<10 papules/pustules, mild erythema, with or without symptoms), moderate (10-19 papules/pustules, moderate erythema, with or without symptoms), or severe (>20 papules/pustules, severe erythema, with or without symptoms). Although the authors state the recommendations are not inclusive of all clinical practice situations, their recommendations are based on thorough literature review and consensus among the authors (Fig 2). Taken together with the above review, the information in the consensus guidelines should provide the clinician with not only a treatment algorithm but also insight into the mechanism of action behind established and emerging therapies.

Emerging therapies

Key points

- **Novel serine protease inhibitors may be useful in treating papulopustular rosacea because they inhibit the cleavage of the cathelicidin precursor into LL-37, the molecule's active form**
- **Although larger scale studies are needed, an initial pilot study suggests that topical application of the mast cell stabilizer cromolyn sodium may be beneficial in treating rosacea because mast cells release known rosacea triggers such as LL-37, matrix metalloproteases, and inflammatory cytokines**

Topical serine protease inhibitors. As discussed in part I of this continuing medical education article, individuals with rosacea have high levels of the serine protease KLK5.⁷⁵ KLK5 cleaves the cathelicidin precursor into LL-37, its active form. Abnormally high levels of KLK5 are thought to contribute to the increased levels of cathelicidin that play a role in the pathogenesis of rosacea.⁷⁶ Inhibiting KLK5 would therefore serve as a therapeutic option in rosacea, and these findings have been confirmed in studies showing that 15% azelaic acid gel decreases expression of KLK5 and LL-37 in lesional rosacea skin (Fig 1). To further investigate the role of serine protease inhibitors in rosacea, 1 study looked at the efficacy of topical epsilon-aminocaproic acid (ACA), a serine protease inhibitor currently approved by the FDA for promoting hemostasis, in patients with PPR.⁷⁷ As early as 6 weeks after treatment initiation, subjects assigned to the ACA group had a statistically

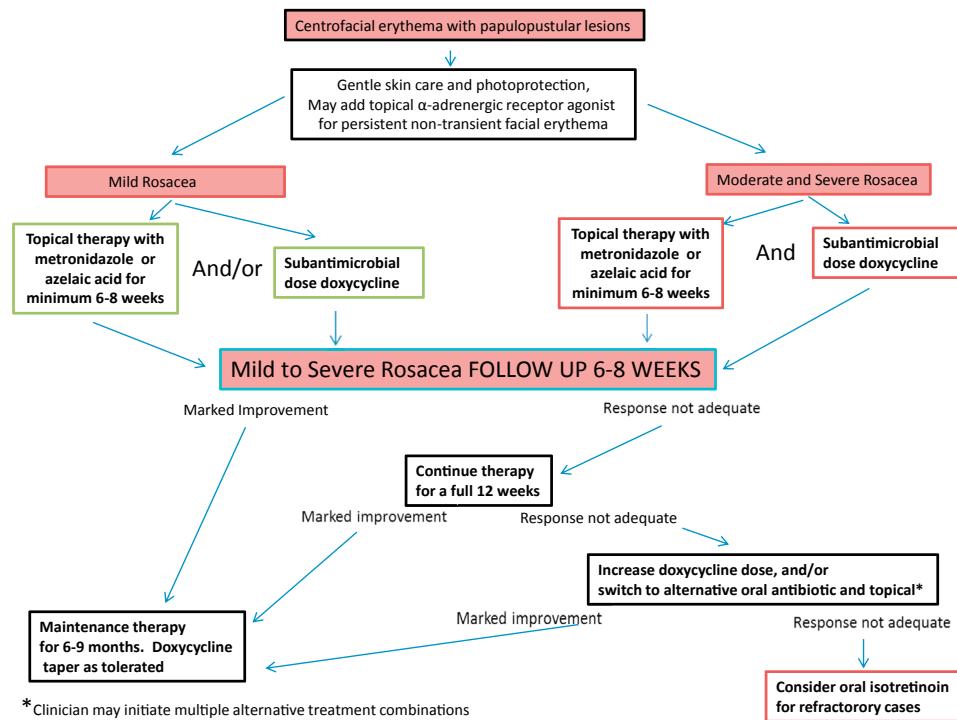


Fig 2. Recommended treatment plan for rosacea patients. This diagram presents an algorithm for treating rosacea adapted from a recent consensus statement from the Del Rosso et al.⁷⁴

significant reduction in serine protease activity compared to the control group. This difference persisted throughout the 12-week duration of the study. At week 12, subjects in the treatment group also had reduced erythema scores compared to those in the control group, further suggesting a therapeutic role for serine protease inhibitors in treating rosacea.

Mast cell stabilizers. Mast cells have been suggested to play a role in mediating the cathelicidin-induced inflammation found in rosacea by releasing LL-37, MMPs, and inflammatory cytokines.^{78,79} Blocking mast cell degranulation was therefore hypothesized to be a potential therapeutic target in rosacea, and this hypothesis was recently tested in a small, randomized controlled trial using the mast cell stabilizer cromolyn sodium. Ten adults with ETR were randomized to apply either cromolyn sodium 4% solution or a vehicle solution alone to their face twice daily.⁸⁰ After 8 weeks, facial erythema and MMP, cathelicidin, and KLK5 levels had decreased in the treatment group, with MMP levels decreasing significantly compared to controls. Although larger trials are needed to confirm these data, these findings suggest that cromolyn sodium may be useful in treating ETR.

DISCUSSION

Patient education, skin care, and pharmacologic treatments are all pillars of effective and comprehensive

management of rosacea. With recent advances in the understanding of the pathogenesis of rosacea, more opportunities for therapeutic interventions are being discovered. In addition to the antiinflammatory and antioxidant effects of current topical and systemic medications, new therapies, such as serine protease inhibitors and mast cell stabilizers, may also improve rosacea symptoms. Approaching treatment through both standard and novel pathways while focusing on patient education and skin care can allow for better symptom control and improved quality of life for individuals with rosacea.

REFERENCES

- Aksøy B, Altaykan-Hapa A, Egemen D, Karagoz F, Atakan N. The impact of rosacea on quality of life: effects of demographic and clinical characteristics and various treatment modalities. *Br J Dermatol.* 2010;163:719-725.
- Gupta MA, Gupta AK, Chen SJ, Johnson AM. Comorbidity of rosacea and depression: an analysis of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey—outpatient department data collected by the U.S. National Center for Health Statistics from 1995 to 2002. *Br J Dermatol.* 2005;153:1176-1181.
- Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol.* 2004;51:499-512.
- Baldwin HE. Diagnosis and treatment of rosacea: state of the art. *J Drugs Dermatol.* 2012;11:725-730.
- Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46:584-587.

6. Dirschka T, Tronnier H, Folster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br J Dermatol.* 2004;150:1136-1141.
7. Laquieze S, Czernielewski J, Baltas E. Beneficial use of Cetaphil moisturizing cream as part of a daily skin care regimen for individuals with rosacea. *J Dermatolog Treat.* 2007;18:158-162.
8. Hawkins SS, Subramanyan K, Liu D, Bryk M. Cleansing, moisturizing, and sun-protection regimens for normal skin, self-perceived sensitive skin, and dermatologist-assessed sensitive skin. *Dermatol Ther.* 2004;17(suppl 1):63-68.
9. Del Rosso JQ. Advances in understanding and managing rosacea: part 1: connecting the dots between pathophysiological mechanisms and common clinical features of rosacea with emphasis on vascular changes and facial erythema. *J Clin Aesthet Dermatol.* 2012;5:16-25.
10. Del Rosso JQ. Advances in understanding and managing rosacea: part 2: the central role, evaluation, and medical management of diffuse and persistent facial erythema of rosacea. *J Clin Aesthet Dermatol.* 2012;5:26-36.
11. Mc Aleer MA, Lacey N, Powell FC. The pathophysiology of rosacea. *G Ital Dermatol Venereol.* 2009;144:663-671.
12. Oztas MO, Balk M, Oguş E, Bozkurt M, Oguş IH, Ozer N. The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin Exp Dermatol.* 2003;28:188-192.
13. Jones DA. Rosacea, reactive oxygen species, and azelaic acid. *J Clin Aesthet Dermatol.* 2009;2:26-30.
14. Narayanan S, Hunerbein A, Getie M, Jackel A, Neubert RH. Scavenging properties of metronidazole on free oxygen radicals in a skin lipid model system. *J Pharm Pharmacol.* 2007;59:1125-1130.
15. Briganti S, Flori E, Mastrofrancesco A, et al. Azelaic acid reduced senescence-like phenotype in photo-irradiated human dermal fibroblasts: possible implication of PPARgamma. *Exp Dermatol.* 2013;22:41-47.
16. Del Rosso JQ, Baldwin H, Webster G, American A, Rosacea S. American Acne & Rosacea Society rosacea medical management guidelines. *J Drugs Dermatol.* 2008;7:531-533.
17. Odom R, Dahl M, Dover J, et al. Standard management options for rosacea, part 1: overview and broad spectrum of care. *Cutis.* 2009;84:43-47.
18. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 1: a status report on the disease state, general measures, and adjunctive skin care. *Cutis.* 2013;92:234-240.
19. Del Rosso JQ. A status report on the medical management of rosacea: focus on topical therapies. *Cutis.* 2002;70:271-275.
20. Del Rosso JQ. Medical treatment of rosacea with emphasis on topical therapies. *Expert Opin Pharmacother.* 2004;5:5-13.
21. Del Rosso JQ. Evaluating the role of topical therapies in the management of rosacea: focus on combination sodium sulfacetamide and sulfur formulations. *Cutis.* 2004;73:29-33.
22. van Zuuren EJ, Kramer SF, Carter BR, Gruber MA, Fedorowicz Z. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. *Br J Dermatol.* 2011;165:760-781.
23. Nielsen PG. Treatment of rosacea with 1% metronidazole cream. A double-blind study. *Br J Dermatol.* 1983;108:327-332.
24. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol.* 1987;123:609-614.
25. Breneman DL, Stewart D, Hevia O, Hino PD, Drake LA. A double-blind, multicenter clinical trial comparing efficacy of once-daily metronidazole 1 percent cream to vehicle in patients with rosacea. *Cutis.* 1998;61:44-47.
26. Lowe NJ, Henderson T, Millikan LE, Smith S, Turk K, Parker F. Topical metronidazole for severe and recalcitrant rosacea: a prospective open trial. *Cutis.* 1989;43:283-286.
27. Dahl MV, Jarratt M, Kaplan D, Tuley MR, Baker MD. Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol.* 2001;45:723-730.
28. Dahl MV, Katz HI, Krueger GG, et al. Topical metronidazole maintains remissions of rosacea. *Arch Dermatol.* 1998;134:679-683.
29. van Zuuren EJ, Kramer S, Carter B, Gruber MA, Fedorowicz Z. Interventions for rosacea. *Cochrane Database Syst Rev.* 2011;3:CD003262.
30. Jansen T, Plewig G. Clinical and histological variants of rhinophyma, including nonsurgical treatment modalities. *Facial Plast Surg.* 1998;14:241-253.
31. Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulo-pustular rosacea. *Acta Derm Venereol.* 1999;79:456-459.
32. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol.* 2003;48:836-845.
33. Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. *Arch Dermatol Res.* 1991;283:162-166.
34. Coda AB, Hata T, Miller J, et al. Cathelicidin, kallikrein 5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. *J Am Acad Dermatol.* 2013;69:570-577.
35. Rahman MQ, Ramaesh K, Montgomery DM. Brimonidine for glaucoma. *Expert Opin Drug Saf.* 2010;9:483-491.
36. Fowler J, Jarratt M, Moore A, et al. Once-daily topical brimonidine tartrate gel 0.5% is a novel treatment for moderate to severe facial erythema of rosacea: results of two multicentre, randomized and vehicle-controlled studies. *Br J Dermatol.* 2012;166:633-641.
37. Fowler J Jr, Jackson M, Moore A, et al. Efficacy and safety of once-daily topical brimonidine tartrate gel 0.5% for the treatment of moderate to severe facial erythema of rosacea: results of two randomized, double-blind, and vehicle-controlled pivotal studies. *J Drugs Dermatol.* 2013;12:650-656.
38. Ilkovitch D, Pomerantz RG. Brimonidine effective but may lead to significant rebound erythema. *J Am Acad Dermatol.* 2014;70:e109-e110.
39. Routt ET, Levitt JO. Rebound erythema and burning sensation from a new topical brimonidine tartrate gel 0.33%. *J Am Acad Dermatol.* 2014;70:e37-e38.
40. Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective alpha1-adrenergic receptor agonist, oxymetazoline. *Arch Dermatol.* 2007;143:1369-1371.
41. Bhawan J. Short- and long-term histologic effects of topical tretinoin on photodamaged skin. *Int J Dermatol.* 1998;37:286-292.
42. Weinstein GD, Nigra TP, Pochi PE, et al. Topical tretinoin for treatment of photodamaged skin. A multicenter study. *Arch Dermatol.* 1991;127:659-665.

43. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci.* 2009;55:77-81.
44. Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: all-trans retinoic acid down-regulates TLR2 expression and function. *J Immunol.* 2005;174:2467-2470.
45. Ertl GA, Levine N, Kligman AM. A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol.* 1994;130:319-324.
46. Freeman SA, Moon SD, Spencer JM. Clindamycin phosphate 1.2% and tretinoin 0.025% gel for rosacea: summary of a placebo-controlled, double-blind trial. *J Drugs Dermatol.* 2012;11:1410-1414.
47. Kim MB, Kim GW, Park HJ, et al. Pimecrolimus 1% cream for the treatment of rosacea. *J Dermatol.* 2011;38: 1135-1139.
48. Bamford JT, Elliott BA, Haller IV. Tacrolimus effect on rosacea. *J Am Acad Dermatol.* 2004;50:107-108.
49. Weissenbacher S, Merkl J, Hildebrandt B, et al. Pimecrolimus cream 1% for papulopustular rosacea: a randomized vehicle-controlled double-blind trial. *Br J Dermatol.* 2007; 156:728-732.
50. Karabulut AA, Izol Serel B, Eksioglu HM. A randomized, single-blind, placebo-controlled, split-face study with pimecrolimus cream 1% for papulopustular rosacea. *J Eur Acad Dermatol Venereol.* 2008;22:729-734.
51. Gupta AK, Chow M. Pimecrolimus: a review. *J Eur Acad Dermatol Venereol.* 2003;17:493-503.
52. Grassberger M, Steinhoff M, Schneider D, Luger TA. Pimecrolimus—an anti-inflammatory drug targeting the skin. *Exp Dermatol.* 2004;13:721-730.
53. Forstinger C, Kittler H, Binder M. Treatment of rosacea-like demodicidosis with oral ivermectin and topical permethrin cream. *J Am Acad Dermatol.* 1999;41:775-777.
54. Larios G, Alevizos A, Perimeni D, Rigopoulos D, Katsambas A. Rosacea-like demodicidosis. *Lancet Infect Dis.* 2008;8:804.
55. Kocak M, Yagli S, Vahapoglu G, Eksioglu M. Permethyl 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. *Dermatology.* 2002;205:265-270.
56. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol.* 2008;7: 573-576.
57. Akhyani M, Ehsani AH, Ghiasi M, Jafari AK. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. *Int J Dermatol.* 2008; 47:284-288.
58. Del Rosso JQ, Preston NJ, Caveney SW, Gottschalk RW. Effectiveness and safety of modified-release doxycycline capsules once daily for papulopustular rosacea monotherapy results from a large community-based trial in subgroups based on gender. *J Drugs Dermatol.* 2012;11:703-707.
59. Alexis AF, Webster G, Preston NJ, Caveney SW, Gottschalk RW. Effectiveness and safety of once-daily doxycycline capsules as monotherapy in patients with rosacea: an analysis by Fitzpatrick skin type. *J Drugs Dermatol.* 2012;11:1219-1222.
60. McKeage K, Deeks ED. Doxycycline 40 mg capsules (30 mg immediate-release/10 mg delayed-release beads): anti-inflammatory dose in rosacea. *Am J Clin Dermatol.* 2010; 11:217-222.
61. Kanada KN, Nakatsuji T, Gallo RL. Doxycycline indirectly inhibits proteolytic activation of tryptic kallikrein-related peptidases and activation of cathelicidin. *J Invest Dermatol.* 2012;132:1435-1442.
62. Wise RD. Submicrobial doxycycline and rosacea. *Compr Ther.* 2007;33:78-81.
63. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin.* 2007;25:133-135.
64. Korting HC, Schollmann C. Tetracycline actions relevant to rosacea treatment. *Skin Pharmacol Physiol.* 2009;22:287-294.
65. Craige H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J Am Acad Dermatol.* 2005;53:881-884.
66. Hsu CC, Lee JY. Carvedilol for the treatment of refractory facial flushing and persistent erythema of rosacea. *Arch Dermatol.* 2011;147:1258-1260.
67. Hsu CC, Lee JY. Pronounced facial flushing and persistent erythema of rosacea effectively treated by carvedilol, a nonselective beta-adrenergic blocker. *J Am Acad Dermatol.* 2012;67:491-493.
68. Kennedy Carney C, Cantrell W, Elewski BE. Rosacea: a review of current topical, systemic and light-based therapies. *G Ital Dermatol Venereol.* 2009;144:673-688.
69. Park H, Del Rosso JQ. Use of oral isotretinoin in the management of rosacea. *J Clin Aesthet Dermatol.* 2011;4:54-61.
70. Erdogan FG, Yurtseven P, Aksoy D, Eskioglu F. Efficacy of low-dose isotretinoin in patients with treatment-resistant rosacea. *Arch Dermatol.* 1998;134:884-885.
71. Gollnick H, Blume-Peytavi U, Szabó EL, et al. Systemic isotretinoin in the treatment of rosacea - doxycycline- and placebo-controlled, randomized clinical study. *J Dtsch Dermatol Ges.* 2010;8:505-515.
72. Morizane S, Yamasaki K, Kabigting FD, Gallo RL. Kallikrein expression and cathelicidin processing are independently controlled in keratinocytes by calcium, vitamin D(3), and retinoic acid. *J Invest Dermatol.* 2010;130:1297-1306.
73. Dispenza MC, Wolpert EB, Gilliland KL, et al. Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. *J Invest Dermatol.* 2012;132:2198-2205.
74. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 5: a guide on the management of rosacea. *Cutis.* 2014;93:134-138.
75. Yamasaki K, Schauber J, Coda A, et al. Kallikrein-mediated proteolysis regulates the antimicrobial effects of cathelicidins in skin. *FASEB J.* 2006;20:2068-2080.
76. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13:975-980.
77. Two AM, Hata TR, Nakatsuji T, et al. Reduction in serine protease activity correlates with improved rosacea severity in a small, randomized pilot study of a topical serine protease inhibitor. *J Invest Dermatol.* 2014;134:1143-1145.
78. Di Nardo A, Vitiello A, Gallo RL. Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. *J Immunol.* 2003;170: 2274-2278.
79. McLachlan JB, Shelburne CP, Hart JP, et al. Mast cell activators: a new class of highly effective vaccine adjuvants. *Nat Med.* 2008;14:536-541.
80. Muto Y, Wang Z, Vandenberghe M, Two A, Gallo RL, Di Nardo A. Mast cells are key mediators of cathelicidin initiated skin inflammation in rosacea. *J Invest Dermatol.* 2014;134: 2728-2736.

Practical application of new technologies for melanoma diagnosis

Part I. Noninvasive approaches

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Learning objectives

After completing this learning activity participants should be able to identify new *in situ* technologies that may facilitate melanoma diagnosis; explain the advantages and disadvantages of each new *in situ* technology and how it could impact their patient population; and describe how these technologies can be incorporated into their practice, especially in the screening of patients at high risk of melanoma.

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Confirming a diagnosis of cutaneous melanoma requires obtaining a skin biopsy specimen. However, obtaining numerous biopsy specimens—which often happens in patients with increased melanoma risk—is associated with significant cost and morbidity. While some melanomas are easily recognized by the naked eye, many can be difficult to distinguish from nevi, and therefore there is a need and opportunity to develop new technologies that can facilitate clinical examination and melanoma diagnosis. In part I of this 2-part continuing medical education article, we will review the practical applications of emerging technologies for noninvasive melanoma diagnosis, including mobile (smartphone) applications, multispectral imaging (ie, MoleMate and MelaFind), and electrical impedance spectroscopy (Nevisense). (J Am Acad Dermatol 2015;72:929-41.)

Key words: MelaFind; melanoma; mobile app; MoleMate; Nevisense; spectroscopy; teledermatology.

OPPORTUNITY TO IMPROVE MELANOMA SCREENING EFFICIENCY

Key points

- Melanomas may be difficult to distinguish clinically from nevi, particularly in high-risk patients

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Abbreviations used:

EIS:	electrical impedance spectroscopy
FDA:	US Food and Drug Administration
MSI:	multispectral imaging
SIA:	spectrophotometric intracutaneous analysis
SK:	seborrheic keratosis

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- **Numerous biopsy specimens associated with melanoma screening can be associated with significant costs and patient morbidity**

Making the clinical diagnosis of melanoma can be straightforward when confronted with a lesion that is markedly asymmetric with nonuniform pigmentation, particularly if there is history of recent change in appearance (ie, ABCDE of melanoma¹) or if the atypical lesion is solitary or looks different from all other lesions (ie, ugly duckling²). However, in patients with numerous and clinically atypical nevi, it can be challenging to visually identify the lesion with the greatest histologically atypical features that may represent a new or developing melanoma. The number of nevi needed to remove in order to find 1 melanoma has been used as a measure of melanoma screening efficiency, with nevus to melanoma ratios ranging from 30 for general practitioners^{3,4} to 4 to 12 for dermatologists^{3,5-8} to 5 to 17 in specialized clinics seeing high-risk patients.⁸⁻¹¹ While lower nevus to melanoma ratios may indicate that fewer unnecessary biopsy specimens are being obtained, the optimal ratio for any practitioner or group of patients is unclear because removing too few nevi will likely be associated with missing some melanomas. On the other hand, unnecessary procedures may add significant cost to the medical system and morbidity for patients in the form of discomfort and scarring.

NONINVASIVE TECHNOLOGIES TO FACILITATE MELANOMA DIAGNOSIS

Key points

- Noninvasive technologies may facilitate melanoma diagnosis and/or may minimize obtaining biopsy specimens from benign lesions
- Applications of new technologies may soon impact dermatology

Noninvasive methods and technologies may [F1-4/C]facilitate early melanoma detection (Fig 1). Dermoscopy is a useful adjunctive tool that can help identify melanocytic lesions, increase confidence that a lesion may be benign or malignant, and increase diagnostic sensitivity in experienced users.¹² Serial dermoscopic photographs can be used (with devices such as MoleMax II) to observe individual lesions over time to identify potentially suspicious changes (rapid or asymmetric growth),¹³⁻¹⁷ and the use of total body photography can increase the specificity of screening by confirming that most nevi are stable and not changing.^{9,18-20} In addition to these conventional approaches, a number of noninvasive technologies have been developed that may facilitate a clinical diagnosis of melanoma. Reflectance confocal microscopy allows near-

microscopic visualization of structures below the skin surface that approximates the resolution of histologic examination,^{21,22} and several studies have shown its potential utility.²³⁻²⁵ However, the large size and cost (\$70,000-100,000) of instruments such as the Vivascope (personal communication with manufacturer, March 2015) will likely limit their current use to research applications, and this modality appears unlikely to make its way into community dermatology practices in the near future. These methods and technologies were reviewed in a continuing medical education article dealing with strategies for clinical management of patients with nevi that was published in the *Journal* in 2009.²⁶ Since that time, new information has been presented that addresses the applicability and efficacy of other technologies. In addition, Internet-based mobile applications (apps) have been developed for the detection of melanoma. We focus on these newer noninvasive technologies and their respective applications that are currently (or will soon be) commercially available and that may impact the practice of dermatology.

MOBILE (SMARTPHONE) APPLICATIONS

Key points

- Smartphone-based applications for skin monitoring and melanoma detection are commercially available
- Many smartphone-based apps may not be reliable

The near universal acceptance of the smartphone in developed countries has the potential to impact melanoma screening and early detection. Of 229 dermatology-related apps recently surveyed, 41 (18%) were related to self-surveillance/diagnosis and 8 (3.5%) related to teledermatology; half were free, and the others ranged in price from \$0.99 to \$139.99.²⁷ These include apps developed to assist patients in identifying melanoma on their skin. We reviewed apps that have been validated in published studies (Table 1). Apps and accessories, including dermoscopes that can be mounted on the iPhone (Apple, Cupertino, CA), are also available to facilitate mobile teledermatology. These advancements in mobile technology could improve the detection rate and efficiency of self-skin examinations, leading to reduced time to diagnosis, mortality, and health care costs associated with melanoma. However, concerns have been expressed regarding the safety and accuracy of these mobile technologies.

In 2011, Health Discovery Corporation launched MelApp for the iPhone. It was one of the first mobile apps to use pattern recognition software and mathematical algorithms to provide melanoma risk

Technology	Study	Lesions (melanomas)	Sensitivity (%)	Specificity (%)
SIAscopy	Moncrieff et al. ⁴⁵ Haniffa et al. ⁴⁷ Glud et al. ⁴⁸ Tomatis ⁴⁹ Carrera ⁵⁰	348 (52) 881 (31) 83 (12) 1391 (184) 1966 (287)	83 87 100 80 88	80 91 59 76 80
MelaFind	Elbaum et al. ⁵⁷ Friedman et al. ⁵⁸ Monheit et al. ⁵⁹ Wells et al. ⁶⁰ Hauschild et al. ⁶³	246 (63) 99 (49) 1632 (127) 47 (23) 130 (65)	95 98 98 96 96	68 44 11 8 9
Nevisense	Glickman et al. ⁶⁸ Har-Shai et al. ⁶⁹ Aberg et al. ⁷⁰ Aberg et al. ⁷¹ Aberg et al. ⁷² Mohr et al. ⁷³ Algorithm 1 Algorithm 2 Malvehy et al. ⁷⁴	178 (12) 449 (69) 511 (16) 99 (13) 210 (62) 780 (103) 715 (162) 1946 (265)	92 91 100 92 95 98 99 97	67 64 75 80 49 24 25 34

Fig 1. Noninvasive imaging technologies and their performance in melanoma detection. Figures appear courtesy of (top to bottom) MedX Health Corp, MELA Sciences, and SciBase AB.

Table I. Mobile apps for melanoma detection

Study	Approach	No. of lesions	Melanomas	Sensitivity	Specificity
Robson et al ²⁸	AA	35*	2	50%	88%
Ferrero et al ²⁹	AA	93	93	11%	—
Wolf et al ³¹	188	60			
App 1	AA		70%	40%	
App 2	AA		69%	37%	
App 3	AA		6.8%	94%	
App 4	TD		98%	30%	
Massone et al ³³	TD	18	2	100%	94%
Kroemer et al ³⁴	TD	104	6	100%	97%
Borwe et al ³⁵	TD	69	12	61%†	—

AA, Automated analysis; TD, teledermatology.

*Fourteen of 35 lesions could not be analyzed by the app.

†Presented as diagnostic accuracy rather than sensitivity.

assessments for skin lesions. Robson et al²⁸ used the app to collect risk assessment data for 35 pigmented skin lesions from 31 patients who had been referred to their urgent skin cancer clinic. The app could not assess 40% of the lesions for technical reasons. When

the low- and high-risk assessments reported by MelApp were compared with the histologic and/or clinical diagnoses for the remaining 21 lesions, the calculated sensitivity was 50% and the specificity was 88%. The authors concluded that mobile apps for the risk assessment of melanomas should be used with caution. MelApp is no longer available for download.

SkinScan also launched in 2011. Developed to analyze iPhone photos, it uses a proprietary fractal-based mathematical algorithm to build structural maps and determine the different growth patterns of skin lesions and the surrounding tissue. If SkinScan identifies a “high-risk” skin lesion, then the user is advised to visit the doctor “soon.” The app recommends that “medium” and “low” risk skin lesions be tracked and shown to a physician during an annual skin examination. Ferrero et al²⁹ used SkinScan to evaluate 93 photos of biopsy-proven melanomas. The app reported 11% of the melanomas as high risk, 88% as medium risk, and 1% as low risk, and was unable to analyze some lesions (11% of total). In 2012, SkinScan was rebranded as SkinVision and the algorithm was modified. A clinical trial is planned in Europe to compare SkinVision with traditional diagnostic tools.³⁰ Given the recent changes in the regulation of mobile apps

(discussed below), the nevus analysis algorithm is currently unavailable in the United States.

In perhaps the largest study of its kind, Wolf et al³¹ examined the accuracy of 4 (unidentified) smartphone apps that were used to evaluate images of 188 skin lesions, which included a total of 60 melanomas (44 invasive and 16 in situ) and 128 benign lesions (including nevi, seborrheic keratoses [SK], lentigos, dermatofibromas, and hemangiomas). The 4 apps were able to analyze 85% to 98% of the images, with sensitivities ranging from 7% to 98% and specificities ranging from 30% to 94%. The apps with the lowest sensitivities used automated algorithms to analyze the images; the best performing program missed 18 of 60 (30%) melanomas, whereas the app with the highest sensitivity used a store-and-forward form of mobile teledermatology (ie, images were analyzed by a remote dermatologist). In a related correspondence, Stoecker et al³² questioned why the accuracy of this mobile teledermatology-based app exceeded what has been previously reported for teledermatology, and pointed out that the proportion of melanoma in situ to invasive melanoma lesions used in the study was much lower than is routinely seen in dermatology clinics or pigmented lesion centers—suggesting that the low sensitivity of smartphone apps is all the more worrisome.

Use of mobile teledermatology for melanoma screening

Key points

- Mobile teledermatology appears to be feasible for melanoma screening
- Studies comparing mobile teledermatology with face to face dermatologic consultation and histopathologic examination are limited
- Smartphone apps are not designed to grade nevi or perform comparative analysis

Several studies specifically evaluated the use of mobile teledermatology in melanoma screening. Massone et al³³ used a smartphone with a built-in 2-megapixel camera and pocket dermoscope to acquire clinical and dermoscopic images of 18 pigmented skin lesions (16 nevi and 2 melanomas) that were then forwarded to 2 independent (tele-) dermatologists for evaluation. Compared to the face to face diagnoses, the 2 teleconsultants correctly identified 89% and 91.5% of the lesions based on clinical and dermoscopic images, respectively. In a follow-up study, Kroemer et al³⁴ used a smartphone with a built-in 3.2-megapixel camera and pocket dermoscope to obtain clinical and dermoscopic images of 104 skin lesions (including 6 melanomas) from 80 patients. A single teledermatologist

reviewed each set of clinical and dermoscopic images separately (1 month apart) and recorded a diagnosis. When differentiating benign from malignant skin lesions, the concordance between the teledermatologist and histopathology was 90% (κ value, 0.84) for both clinical and dermoscopic images. In addition, the teledermatologist and a face to face dermatologist were able to categorize all the melanomas as malignant melanocytic tumors. Considering all the lesions, the teledermatologist misdiagnosed 26 of the skin tumors, whereas the face to face dermatologist misdiagnosed 11 of the tumors. In a subsequent study, Borve et al³⁵ used a smartphone to capture clinical and dermoscopic images of 69 skin lesions (including 5 invasive melanomas and 7 melanomas in situ) scheduled for excision. The dermoscopic images were obtained using a dermoscope designed specifically as a smartphone attachment. The smartphone was also enabled with iDoc24 (iDoc24; Stockholm, Sweden), an app designed to facilitate mobile teledermatology. Two teledermatologists used a secure Internet platform (Tele-Dermis) to independently view the images. The authors reported that the diagnostic accuracy of the face to face dermatologic evaluation (67%) was similar to one of the teledermatologists (61%), but was statistically better than the other (51%). There was no statistical difference between the face to face dermatologist and the 2 teledermatologists when classifying lesions as benign or malignant.

These studies suggest that mobile teledermatology could potentially be used as a triage system for pigmented skin lesions, to screen referrals from primary care physicians, or be used in large-scale melanoma screening. In addition, such a platform may facilitate self-skin examinations. For example, Janda et al³⁶ provided a small group of high-risk patients with a mobile teledermoscope, which consisted of an iPhone 3 (with app preloaded) attached to a Handyscope (FotoFinder Systems; Bad Birnbach, Germany), and instructions for photographing and e-mailing the photographs to researchers. Patients selected both atypical and nonatypical appearing nevi, indicating the need for more training. Only 58 of 66 (88%) patient photographs were evaluable, with the remainder being of poor quality. In a follow-up study, 22 patients performed self-skin examinations assisted by mobile teledermatology and then underwent clinical examination; 1 melanoma and several nonmelanoma skin cancers were missed by patients and detected by the clinicians.³⁷ It was noted that patients tended not to select lesions in sexually sensitive areas or areas that are more difficult to

see. Patient omission of potential melanomas during lesion selection is further evidenced by Viola et al,³⁸ who found that a significant number of melanomas were incidentally identified by the consulting dermatologist in addition to the primary lesion of concern.

It is critical to note that smartphone apps and teledermatology are an adjunct to regular total body skin examinations, not a replacement for them. A limitation of mobile teledermatology is that clinical examination by the dermatologist is restricted to lesions of patient concern; face to face visits provide opportunities for complete skin examinations that may reveal skin cancers not noticed by the patient. Finally, another limitation of mobile apps is that they are generally not designed to grade nevus atypia or perform comparative analysis. They tend to provide an “all or nothing” answer on individual lesions (ie, nevus vs melanoma) without indicating the degree of irregularity or other potentially suspicious features. In addition, one of the major drawbacks over a face to face encounter is that these apps are not designed to compare lesions to one another, to identify the most atypical lesion (ie, ugly duckling), or to recognize atypical lesions that have shared features (ie, signature nevi).

Regulation of mobile technologies

Key point

- **The US Food and Drug Administration has regulatory authority over mobile apps, but the extent to which regulations will be enforced is unclear**

The US Food and Drug Administration (FDA), under the guidance of the US Congress, has expressed the intent to regulate mobile medical apps designed to diagnose, treat, mitigate, or prevent disease. In 2011, the FDA proposed guidelines to regulate mobile apps in accordance with existing regulated devices if the program (1) transforms the mobile device to function in a manner similar to existing FDA-regulated devices or (2) allows the device to connect or act accessory to preexisting FDA-regulated devices or programs.^{39,40} Regulations for apps that pose minimal risk to patients and consumers but meet regulatory criteria for categorization as a “device” will not require submission for premarket review for approval by the FDA. These guidelines were officially issued in September 2013, and updated subsequently. Regulated mobile medical apps will include those that assist with self-management without providing specific treatment suggestions and devices that document, show, or communicate medical conditions to health care

providers.⁴¹ It is unclear how “minimal risk” will be defined and whether it will be applicable to devices used to rule out potential skin malignancy.

In summary, screening for melanoma with mobile devices appears feasible, with direct patient to physician teledermatology holding the most promise. However, barriers exist in the risk of missed malignancies (through the omission of malignant lesions not presented by the patient) and implementation of device regulations. Future investigation should focus on demonstrating the efficacy of mobile apps in melanoma detection as they are intended to be used by the population. If these apps prove unreliable, they may potentially cause harm to patients. We look forward to new developments that may enhance mobile technology and additional controlled studies that may validate it.

MULTISPECTRAL IMAGING: SPECTROPHOTOMETRIC INTRACUTANEOUS ANALYSIS (SIAsCOPY) Spectrophotometric intracutaneous analysis technology and agreement with histologic features

Key points

- **SIAscopy uses chromophore imaging to determine microscopic architecture**
- **SIAscopy may assess melanin content and larger collagen structures more accurately than hemoglobin, but may not directly correlate with histology**

Spectrophotometric intracutaneous analysis (SIA) is a noninvasive multispectral imaging (MSI) technology intended for the evaluation of pigmented skin lesions and the detection of melanoma. A handheld scanner (SIAscope) illuminates 1.2 to 2.4 cm² areas of skin with wavelengths of light ranging from 400 to 1000 nm. Newer versions of the SIAscope are also capable of capturing dermoscopic images. Calibrated images are analyzed by a series of algorithms that extract information about the distribution, position, and quantity of several different chromophores (ie, eumelanin, hemoglobin, and collagen). Several studies have investigated the accuracy of SIAscopy in displaying the amount of melanin, blood, and collagen present in the epidermis and dermis. Claridge et al⁴² found almost perfect correlation for melanin and a moderate correlation for hemoglobin. Subsequently, Matts et al⁴³ found that eumelanin measurements obtained by SIAscopy correlated with melanin density in histologic samples across all Fitzpatrick skin types. However, Terstappen et al⁴⁴ subsequently compared the SIAscopic images of 60 suspicious pigmented

skin lesions with their histopathologic features, and found that dermal melanin and collagen holes had no agreement with histologic results.

Early clinical studies using SIAscopy

Key points

- **Multiple studies have assessed the sensitivity and specificity of SIAscopy in melanoma detection**
- **SIAscopy may not be superior to dermoscopy**
- **SIAscopy is not well-suited for seborrheic keratoses, which may limit its utility in primary care settings**

Moncrieff et al⁴⁵ used a SIAscope to obtain images of 348 pigmented skin lesions (including 52 melanomas) referred for excision. The presence of dermal melanin, an erythematous blush from blood displacement, and a lesion diameter ≥ 6 mm favored a diagnosis of melanoma over benign lesions with 82.7% sensitivity and 80.1% specificity. In another study, Govindan et al⁴⁶ reported on SIAscopy in the screening of 886 lesions referred to a pigmented lesion clinic by general practitioners. The presence of only dermal melanin gave 94.4% sensitivity and 64% specificity for melanoma detection.

Several studies compared the performance of SIAscopy to dermoscopy. In a study by Haniffa et al,⁴⁷ dermatologists evaluated 881 pigmented lesions (including 31 melanomas) with a dermoscope and then reexamined each lesion using a SIAscope. The sensitivity and specificity of dermoscopy alone was 94% and 91%, respectively, and performance was not improved by the addition of SIAscopy. In another study, Glud et al⁴⁸ compared SIAscopy and dermoscopy in the evaluation of 83 lesions (including 12 melanomas) referred by nondermatologists for treatment. They reported that SIAscopy had higher sensitivity compared to dermoscopy (100% vs 92%), but lower specificity (59% vs 81%).

Several teams have developed new algorithms for MSI. Tomatis et al⁴⁹ developed a neural network classifier using a data set of 1391 lesions (including 184 melanomas) that was able to discriminate between melanomas and nonmelanoma lesions with a sensitivity of 80% and a specificity of 76%. Subsequently, Carrara et al⁵⁰ examined 1966 lesions (including 287 melanomas) excised for histopathologic diagnosis and 1940 nonexcised lesions that were not clinically suspicious by MSI and developed a classifier to differentiate the lesions as “excision-needed” or reassuring, based on the clinicians’ management decisions. The system was able to

emulate the clinicians with a sensitivity of 88% and a specificity of 80%.

These early studies suggested that SIAscopy might be useful for nondermatologists selecting skin lesions for referral because it does not require specific training and expertise. In addition, SIAscopy might be a good tool for training and archiving because it can also capture dermoscopic images. One problem with SIAscopy found in primary care settings is the low performance attributed to the high prevalence of SKs. Several studies^{46,47,51} have reported on the negative effects SKs have on the sensitivity and specificity of SIAscopy.

MoleMate

Key points

- **Alternative algorithms and training programs were developed to improve the diagnostic accuracy of SIAscopy in primary care settings**
- **Molemate demonstrates equivalent sensitivity but reduced specificity compared to traditional diagnostic techniques**
- **MoleMate has received regulatory approval in the United States, European Union, and Canada**

Emery et al⁵² used SIAscopy in the evaluation of 1211 lesions in 858 patients in primary care settings in the United Kingdom and Australia. The original SIAscopic diagnostic algorithm did not perform well in primary care settings because of the high prevalence of SKs and hemangiomas seen in that patient population; therefore, a primary care scoring algorithm was developed that would eventually be called MoleMate. The new algorithm added additional features (ie, the presence of collagen white dots, a cerebriform pattern, and blood vessels) and the patient’s age to the Moncrieff scoring system⁴⁵ to aid in correctly differentiating SKs and hemangiomas from melanoma. The new algorithm proved to be more specific than the Moncrieff scoring system and dermoscopy using the 7-point checklist.

Several studies have shown that training of primary care practitioners can improve performance. Wood et al⁵³ reported that a short, computer-based course significantly improved SIAscopic feature recognition in a group of 25 primary care providers, whose median test scores improved from 74% to 86% after training. Watson et al⁵⁴ evaluated the effectiveness of the training program in a group of 18 general practitioners in the United Kingdom and another 30 in Australia. The United Kingdom and Australian groups

similarly improved their median test scores after completing the training program.

In a large randomized controlled trial, Walter et al⁵⁵ studied the evaluation by primary care physicians of 1297 patients presenting with pigmented skin lesions that were not immediately diagnosed as benign. Approximately half the patients were subjected to best practice (ie, clinical history, naked eye examination, and dermoscopy) while the remaining patients were evaluated using best practice in conjunction with MoleMate. Almost all (17/18) of the confirmed melanomas in the best practice group were correctly diagnosed, while (18/18) of them were correctly identified using best practice combined with MoleMate. For benign lesions, on the other hand, MoleMate was inferior to best practice in recommending a significantly higher percentage of lesions for biopsy.

MoleMate and its expanded features version (SIMSYS) is marketed by MedX Health Corporation (Mississauga, Ontario, Canada). These products received FDA approval in 2011, and have also received Health Canada clearance and CE Mark approval. MoleMate costs \$6000 and SIMSYS costs \$8000, but the latter adds the capability to store information on the patient, lesion location, and previous analysis (personal communication with manufacturer, March 2015). These systems are not broadly used in the United States by dermatologists, but may be having an impact in the cosmetics industry. MedX licensed a version of its technology to Proctor & Gamble for use in cosmetic point of sale counters to show consumers the condition of their skin before and after the use of skin products.

MULTISPECTRAL IMAGING—MELAFIND

MelaFind technology and early studies

Key points

- **MelaFind uses automatic image analysis and pattern recognition of skin lesions to determine morphologic disorganization**
- **Several studies suggest that MelaFind improves biopsy sensitivity but decreases specificity**

MelaFind (MELA Sciences; Irvington, NY) is a noninvasive MSI system that uses a handheld scanner to obtain 10 images using wavelengths ranging from visible to near-infrared (430-950 nm) that penetrate up to 2.5 mm beneath the skin surface.⁵⁶ First, the lesion is separated from the surrounding tissue based on differences in reflectance of blue (430 nm) light (image segmentation).

Next, information regarding the presence and distribution of certain dermoscopic features (eg, asymmetry, blotchiness, etc) is extracted from the images. Finally, automated algorithms, based on linear classifiers, are used to analyze the data and ultimately determine the morphologic disorganization of the lesion. A proprietary database containing images of roughly 10,000 lesions (including >600 melanomas) was used in the training of the classifier. Each algorithm was designed to differentiate melanoma from one of the following: low-grade dysplastic nevus, congenital nevus, common nevus, SK, solar lentigo, and pigmented basal cell carcinoma. A given lesion is assigned 6 different scores, and if all the scores are above a set threshold value, then MelaFind recommends that a biopsy specimen of the lesion be obtained.

Elbaum et al⁵⁷ imaged 246 pigmented lesions (including 63 melanomas) that were considered suspicious for melanoma by skin cancer specialists and that were subsequently referred for biopsy. Two classifiers were used to define the threshold values that were used in separating melanoma from other lesions; a linear classifier yielded 100% sensitivity and 85% specificity, while a nonlinear classifier provided a sensitivity of 95% and a specificity of 68%. In a subsequent study, Friedman et al⁵⁸ independently presented 10 expert dermatologists with dermoscopic images of 99 pigmented skin lesions (including 49 melanomas ≤6 mm) and compared their diagnostic performance and management decisions with those of MelaFind. The dermatologists collectively demonstrated 39% sensitivity and 82% specificity in melanoma diagnosis and 71% sensitivity and 49% specificity in recommending that a biopsy specimen be obtained. MelaFind produced a sensitivity of 98% and a specificity of 44% in recommending a biopsy.

In a large multicenter study, Monheit et al⁵⁹ used MelaFind to evaluate 1632 pigmented lesions (including 127 melanomas) that were referred by dermatologists for biopsy. MelaFind gave a sensitivity of 98% (2 melanomas were missed) and a specificity of 11% in recognizing the melanomas and recommending that a biopsy specimen be obtained. MelaFind was compared to 39 dermatologists in an accompanying reader study consisting of 50 pigmented lesions (including 25 melanomas) selected from the initial pool of 1632 lesions. Dermatologists were presented with clinical history and dermoscopic images yielding a sensitivity of 78%, with fair interreader agreement (κ value, 0.22), but no specificity was reported (available in the package insert). In a follow-up study, Wells et al⁶⁰ randomly selected 47 of the 1632 lesions (which included 23

Table II. Comparison of dermatologist performance without and with use of noninvasive devices

Study	Approach	No. of lesions	Melanomas	Sensitivity	Specificity
MelaFind					
Rigel et al ⁶⁰	Clinical only	24	5	69%	54%
	Clinical plus device			94%	40%
Hauschild et al ⁶¹	Clinical only	130	6	70%	56%
	Clinical plus device			78%	46%
Nevisense					
Har-Shai et al ⁶⁷	Clinical only	400	53	81%	84%
	Clinical plus device			98%	55%

melanomas) and provided clinical history and clinical and dermoscopic images to a panel of dermatologists who were blinded to the MelaFind results. The average biopsy sensitivity and specificity of the participating dermatologists was 80% and 43%, respectively, while sensitivity and specificity of MelaFind was 96% and 8%, respectively. Together, these studies suggest that MelaFind may have increased diagnostic sensitivity but reduced specificity for diagnosing melanoma compared to dermatologists. In addition, it may misclassify non-melanoma skin cancers because the technology is designed to assess overall structural disorganization of lesions rather than atypical cellular features.

Effect of MelaFind on performance of dermatologists

Key points

- The utility of MelaFind for melanoma detection has been debated
- MelaFind as an adjunct to clinical examination increases provider sensitivity but decreases specificity

Melafind has been criticized for its low specificity in melanoma detection, which comes at the expense of its high sensitivity. Cukras⁶¹ expressed reservations about the low specificity of Melafind, suggesting that it may have limited utility; in achieving such high sensitivity it “almost always recommends biopsy.” In regard to the study by Wells et al,⁶⁰ it was argued that randomly obtaining biopsy specimens of the subset of lesions at the same rate in the larger study would also achieve 94% sensitivity and 6% specificity. In the study by Monheit et al,⁵⁹ MelaFind also recommended obtaining a biopsy specimen for >90% (1472/1632) of the lesions.

Several recent studies have investigated the influence of MelaFind on the biopsy decisions reached by dermatologists. While the specificity of the device is low when used in isolation, dermatologists using MelaFind as a clinical adjunctive tool to

assist in the decision to biopsy lesions of concern demonstrated improved specificity, which was still lower than their specificity without the device (Table II). Rigel et al⁶² provided 179 dermatologists with the clinical history and clinical and dermoscopic images of 24 pigmented skin lesions (including 5 melanomas). After the dermatologists decided which lesions they would recommend for biopsy, they were provided the MelaFind recommendations and allowed to change their biopsy decisions. Knowledge of the MelaFind results improved their biopsy sensitivity from 69% to 94%, but their specificity declined from 54% to 40%. In addition, their biopsy recommendation rates associated with lesions that were not recommended by MelaFind for biopsy fell from 43% to 25%. The authors concluded that MelaFind can improve biopsy decision-making by dermatologists.

Recently, Hauschild et al⁶³ performed an online reader study in which 130 German dermatologists were provided the clinical history and clinical and dermoscopic images for 130 pigmented skin lesions (including 65 melanomas), with half of the dermatologists randomly selected to also receive MelaFind results for each lesion. For these lesions, MelaFind had a sensitivity of 96% and a specificity of 9%. The dermatologists without access to MelaFind results had a sensitivity of 70% and specificity of 56%, while those given the MelaFind results had a significantly higher sensitivity of 78% and lower specificity of 46%. The authors suggested that MelaFind could be an effective tool and reasoned that the reduced specificity associated with knowing the results was acceptable given the number of additional early melanomas that were detected by the dermatologists. Although not strictly used as such in the aforementioned studies, the high sensitivity of the device could be useful for ruling out melanoma given its high negative predictive value—although it should be noted that in the study by Monheit et al,⁵⁹ 2 of the lesions not recommended for biopsy by MelaFind proved to be melanoma.

Regulatory approval of MelaFind

Key points

- **MelaFind has received premarket approval from the US Food and Drug Administration and CE Mark approval in the European Union**
- **The US Food and Drug Administration has stipulated that MelaFind be used only by dermatologists to assist in biopsy decision-making**

MelaFind received premarket FDA approval in 2011, but because of concerns about the device's inability to detect nonmelanoma skin cancers and its low specificity, the FDA and MELA Sciences agreed to restrict its use with the following stipulations: (1) MelaFind is intended to assist the dermatologist with his/her decision to biopsy clinically atypical lesions by providing additional morphologic analysis; (2) lesions selected for analysis should not include those for which a melanoma diagnosis is considered likely as biopsy is already indicated; and (3) MelaFind is only to be used by a dermatologist who has completed a training program in the appropriate use of the device.⁶⁴ MelaFind also received approval in the European Union in 2011.

It has been reported that about 150 of the MelaFind devices have been distributed in the United States and Germany.⁶⁴ Under the company's physician lease agreement, a one-time fee of \$10,000 is charged for installation of the device and training of personnel, along with an annual renewal fee of \$2000 plus additional charges for each use.⁶⁵ Health insurance does not currently cover the service, and it is reported that patients are paying \$25 to \$175 for the first lesion evaluation and around \$25 each for subsequent lesions.⁶⁴

ELECTRICAL IMPEDANCE

SPECTROSCOPY

Technology and initial studies

Key points

- **Electrical impedance spectroscopy measures the opposition to alternating electrical currents to determine differences in cellular properties**
- **Electrical impedance spectroscopy devices have improved (ie, TransScan, SciBase II, SciBase III, and Nevisense)**
- **Multiple studies have assessed performance of electrical impedance spectroscopy in melanoma diagnosis**

Electrical impedance spectroscopy (EIS) is a noninvasive diagnostic approach based on

inherent electrical differences between benign and malignant tissues⁶⁶ that was initially investigated in breast cancer screening.⁶⁷ EIS measures electrical resistance within tissues subjected to alternating currents of various frequencies (1 kHz-2.5 MHz). Resistance to low frequencies is affected by the extracellular environment, whereas both the intra- and extracellular environments affect measurements at higher frequencies. Changes in cell shape, size, and membrane composition can be detected by EIS. Scanning uninvolved adjacent tissue allows determination of baseline electrical impedance of skin in a given area, which can then be compared to the electrical impedance of the lesion. An algorithm is used to classify the lesion based on data obtained from both the lesion and the adjacent skin.

Glickman et al⁶⁸ initially tested a TransScan device on human xenografted melanoma tumors in mice, and then used it to evaluate 178 suspicious skin lesions (including 12 melanomas) scheduled for excision. The device had a sensitivity of 92%, and specificity of 67%, although sensitivity improved with increasing melanoma depth. In a follow-up study, Har-Shai et al⁶⁹ used an updated version of TransScan to study 449 lesions (including 69 melanomas) scheduled for excision. The device failed to detect melanomas on the head and the neck because of electrical differences between these areas and the rest of the body. For lesions on the trunk and extremities, the EIS system had a sensitivity of 91% with a specificity of 64%, compared to dermatologists who had a sensitivity of 81% and a specificity of 84%. The addition of EIS to clinical examination improved the physicians' sensitivity to 98% but decreased their specificity to 55%.

Aberg et al⁷⁰ used the SciBase II EIS device (SciBase AB; Stockholm, Sweden) to evaluate 511 nevi and 100 skin cancers (including 16 melanomas) scheduled for excision. SciBase II had 100% sensitivity and 75% specificity in distinguishing melanomas from nevi, and 100% sensitivity and 87% specificity in distinguishing nonmelanoma skin cancers from nevi. In a follow-up study, Aberg et al⁷¹ assessed 99 nevi and 13 melanomas, with the modification of using 2 different electrodes: a completely noninvasive circular electrode and a microinvasive spiked electrode. The small spikes penetrate the stratum corneum to reach the epidermis, and reduce biologic impedance variation that was problematic with earlier devices on the head and neck. The spiked electrodes demonstrated the best performance in distinguishing benign nevi from melanoma, yielding a sensitivity of 92% and a specificity of 80%. In a multicenter study, Aberg

et al⁷² investigated the performance of SciBase II using disposable spiked electrodes and a new automated classification algorithm. The automated algorithm was trained on 285 lesions (including 135 melanomas) and then validated on a different set of 210 lesions (including 62 melanomas). The observed sensitivity was 95% and specificity was 49%, and sensitivity increased with melanoma thickness.

Further improvements were realized in the SciBase III device, which was used in a multicenter study by Mohr et al⁷³ of 681 patients with 751 lesions referred for excision. Based on experiences with SciBase II, 2 different algorithms were developed and evaluated. The first algorithm, in which 40% of the lesions were used for training and the remaining 60% for validation, gave a sensitivity of 98% for melanoma, 100% for nonmelanoma skin cancer, and 84% for severely dysplastic nevi; the overall observed specificity was 24%. The second algorithm, in which 55% of the lesions were used for training and the remaining 45% for validation, gave a sensitivity of 99% for melanoma, 98% for nonmelanoma skin cancer, and 94% for severely dysplastic nevi; the overall observed specificity was 25%. By comparison, the sensitivity was 100% and specificity was 8% for the referring dermatologists.

Nevisense

Key points

- Nevisense has high sensitivity for both melanoma and nonmelanoma skin cancers
- Nevisense received the European CE Mark and approval by the Australian TGA, but has not yet received US Food and Drug Administration approval

Results of performance of the newest SciBase iteration (Nevisense) in a phase 3 multicenter (5 US and 17 European sites) prospective, blinded clinical trial were recently reported by Malvehy et al.⁷⁴ In total, 1951 patients with 2416 lesions were enrolled in the study, with all lesions subsequently excised and evaluated by a panel of dermatopathologists. Ultimately, 473 lesions were excluded for various reasons (eg, investigator errors, lack of consensus diagnosis among the histopathologists, technical issues), which resulted in a total of 1946 evaluable lesions (including 265 melanomas). In addition, clinical and dermoscopic images of 1701 lesions (including 238 melanomas) were obtained for later evaluation by expert dermatologists in a reader-type study. Nevisense classified melanoma with a sensitivity of 97% (9/265 melanomas were missed) and a specificity of 34%. Nevisense had 100% sensitivity for nonmelanoma skin cancers (48 basal

cell carcinomas and 7 squamous cell carcinomas). The dermatologists detected melanoma with a sensitivity of 49% to 61% and a specificity of 89% to 94%. Nevisense has received the European CE Mark and been approved by the Australian TGA, but has not yet been approved by the FDA for use in the United States. Pricing for Nevisense in the United States is not currently available (personal communication with manufacturer, March 2015).

RECOMMENDATIONS

Over the past few years, a number of noninvasive imaging applications and devices to facilitate melanoma detection have become available and are poised to impact the practice of dermatology. These new technologies offer the promise of improving early melanoma detection both by patients and physicians and reducing the practice of obtaining unnecessary biopsy specimens. Although multiple mobile apps have been developed for self-skin examination and appear feasible for skin screening and teledermatology, none of them (based on what is reported in the literature) have been adequately studied and/or shown to be sufficiently accurate and reliable to recommend at this point in time. MSI and EIS technologies have each led to next-generation devices that are easy to use in outpatient clinical settings. While these devices have some advantages and disadvantages, as summarized in Table III, they generally tend to have greater diagnostic sensitivity but lower specificity than has been reported for experienced dermatologists and dermatologists. While dermoscopy by experienced practitioners appears to have a better sensitivity and specificity than any of the devices,¹² it is important to note that no trials have been conducted to compare the performance of dermatologists with or without dermoscopy against dermatologists using any of these newer devices in a true clinical setting. Another important consideration of the low specificity of these tools is that they are likely to recommend obtaining a biopsy specimen of lesions that are already difficult for dermatologists to diagnose (ie, clinically atypical nevi that are not clearly benign or malignant) and therefore may not be as helpful in patients with multiple atypical nevi. None of these devices scan the entire body, as would occur during a complete skin examination. It is also important to know that these devices require the lesion to be on a flat surface and accessible; lesions on the ears and under the nail plate, for example, are not evaluable. In addition, the trials of these devices excluded acral, mucosal, and genital lesions, as well

Table III. Comparison of new-generation noninvasive imaging devices

	MoleMate	MelaFind	Nevisense
Technology	MSI	MSI	EIS
Sensitivity	50%	>95%	>95%
Specificity	80-90%	10%	25%
Detection of NMSC	No	No	Yes
Detection of SK	No	No	Yes
Speed*	<1 min	1-2 min	5-10 min
Approval	US, EU, and Canada	US and EU	EU and Australia
Cost	\$6000	Lease [†]	N/A

Note: MoleMate, MelaFind, and Nevisense are trademarks of their respective manufacturers.

EU, European Union; N/A, not available; NMSC, nonmelanoma skin cancer; SK, seborrheic keratosis; US, United States.

*Approximate time to evaluate single lesion.

[†]2013 leasing agreement stipulates \$10,000 installation and training fee, \$2000 annual renewal fee, and charges per lesion or patient session.

as lesions in hair-bearing areas. Finally, while these devices give a quantitative readout that is objective, there is a subjective component in which lesions the practitioner chooses to evaluate with the device.

In conclusion, while the performance of these devices is to some extent limited by the particular technology, their sensitivity and specificity for melanoma detection are largely determined by the threshold settings used for the algorithm classifiers. It is likely that the fear of missing a melanoma has led to classifier settings that favor high sensitivity at the expense of lower specificity. An interesting question to consider is what standards of performance the industry should be held for such devices in order to ensure patient safety and minimize harm. It is conceivable that the classifiers in these devices may be updated or modified for particular practice settings (such as primary care or general dermatology) and/or for particular patients based on melanoma risk factors, including numbers of nevi and clinically atypical nevi, and patient-reported history regarding individual lesions. Individual practitioners will have to contend with the practical considerations of evaluating how such applications and devices could be incorporated into their practices and be paid for, because their use is currently not covered by most health insurance plans.

REFERENCES

- Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE—an evolving concept in the early detection of melanoma. *Arch Dermatol.* 2005;141:1032-1034.
- Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. *Arch Dermatol.* 1998;134:103-104.
- Marks R, Jolley D, McCormack C, Dorevitch AP. Who removes pigmented skin lesions? *J Am Acad Dermatol.* 1997;36:721-726.
- Hansen C, Wilkinson D, Hansen M, Argenziano G. How good are skin cancer clinics at melanoma detection? Number needed to treat variability across a national clinic group in Australia. *J Am Acad Dermatol.* 2009;61:599-604.
- Chia AL, Simonova G, Dutta B, Lim A, Shumack S. Melanoma diagnosis: Australian dermatologists' number needed to treat. *Australas J Dermatol.* 2008;49:12-15.
- Rolfe HM. Accuracy in skin cancer diagnosis: a retrospective study of an Australian public hospital dermatology department. *Australas J Dermatol.* 2012;53:112-117.
- Sidhu S, Bodger O, Williams N, Roberts DL. The number of benign moles excised for each malignant melanoma: the number needed to treat. *Clin Exp Dermatol.* 2012;37:6-9.
- Argenziano G, Cerroni L, Zalaudek I, et al. Accuracy in melanoma detection: a 10-year multicenter survey. *J Am Acad Dermatol.* 2012;67:54-59.
- Goodson AG, Florell SR, Hyde M, Bowen GM, Grossman D. Comparative analysis of total body and dermatoscopic photographic monitoring of nevi in similar patient populations at risk for cutaneous melanoma. *Dermatol Surg.* 2010;36:1087-1098.
- Salerni G, Carrera C, Lovatto L, et al. Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma. *J Am Acad Dermatol.* 2012;67:e17-e27.
- Moloney FJ, Gutierrez P, Coates E, et al. Detection of primary melanoma in individuals at extreme high risk: a prospective 5-year follow-up study. *JAMA Dermatol.* 2014;150:819-827.
- Braun RP, Rabinovitz HS, Oliviero M, Kopf AW, Saurat JH. Dermoscopy of pigmented skin lesions. *J Am Acad Dermatol.* 2005;52:109-121.
- Kittler H, Pehamberger H, Wolff K, Binder M. Follow-up of melanocytic skin lesions with digital epiluminescence microscopy: patterns of modifications observed in early melanoma, atypical nevi, and common nevi. *J Am Acad Dermatol.* 2000;43:467-476.
- Menzies SW, Gutenev A, Avramidis M, Batrac A, McCarthy WH. Short-term digital surface microscopic monitoring of atypical or changing melanocytic lesions. *Arch Dermatol.* 2001;137:1583-1589.
- Robinson JK, Nickoloff BJ. Digital epiluminescence microscopy monitoring of high-risk patients. *Arch Dermatol.* 2004;140:49-56.
- Haenssle HA, Krueger U, Vente C, et al. Results from an observational trial: digital epiluminescence microscopy follow-up of atypical nevi increases the sensitivity and the chance of success of conventional dermoscopy in detecting melanoma. *J Invest Dermatol.* 2006;126:980-985.
- Fuller SR, Bowen GM, Tanner B, Florell SR, Grossman D. Digital dermoscopic monitoring of atypical nevi in patients at risk for melanoma. *Dermatol Surg.* 2007;33:1198-1206.
- Wang SQ, Kopf AW, Koenig K, Polsky D, Nudel K, Bart RS. Detection of melanomas in patients followed up with total cutaneous examinations, total cutaneous photography, and dermoscopy. *J Am Acad Dermatol.* 2004;50:15-20.
- Feit NE, Dusza SW, Marghoob AA. Melanomas detected with the aid of total cutaneous photography. *Br J Dermatol.* 2004;150:706-714.
- Banky JP, Kelly JW, English DR, Yeatman JM, Dowling JP. Incidence of new and changed nevi and melanomas detected using baseline images and dermoscopy in patients at high risk for melanoma. *Arch Dermatol.* 2005;141:998-1006.

21. Rajadhyaksha M, Gonzalez S, Zavislans JM, Anderson RR, Webb RH. In vivo confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. *J Invest Dermatol.* 1999;113:293-303.
22. Calzavara-Pinton P, Longo C, Venturini M, Sala R, Pellacani G. Reflectance confocal microscopy for in vivo skin imaging. *Photochem Photobiol.* 2008;84:1421-1430.
23. Gerger A, Koller S, Kern T, et al. Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors. *J Invest Dermatol.* 2005;124:493-498.
24. Meyer LE, Otberg N, Sterry W, Lademann J. In vivo confocal scanning laser microscopy: comparison of the reflectance and fluorescence mode by imaging human skin. *J Biomed Opt.* 2006;11:044012.
25. Pellacani G, Guitera P, Longo C, Avramidis M, Seidenari S, Menzies S. The impact of in vivo reflectance confocal microscopy for the diagnostic accuracy of melanoma and equivocal melanocytic lesions. *J Invest Dermatol.* 2007;127:2759-2765.
26. Goodson AG, Grossman D. Strategies for early melanoma detection: approaches to the patient with nevi. *J Am Acad Dermatol.* 2009;60:719-735.
27. Brewer AC, Endly DC, Henley J, et al. Mobile applications in dermatology. *JAMA Dermatol.* 2013;149:1300-1304.
28. Robson Y, Blackford S, Roberts D. Caution in melanoma risk analysis with smartphone application technology. *Br J Dermatol.* 2012;167:703-704.
29. Ferrero NA, Morrell DS, Burkhardt CN. Skin scan: a demonstration of the need for FDA regulation of medical apps on iPhone. *J Am Acad Dermatol.* 2013;68:515-516.
30. Weaver C. Apps Aim to Detect Skin Cancer. *Wall Street Journal.* January 16, 2013.
31. Wolf JA, Moreau JF, Akilov O, et al. Diagnostic inaccuracy of smartphone applications for melanoma detection. *JAMA Dermatol.* 2013;149:422-426.
32. Stoecker WV, Rader RK, Halpern A. Diagnostic inaccuracy of smartphone applications for melanoma detection: representative lesion sets and the role for adjunctive technologies. *JAMA Dermatol.* 2013;149:884.
33. Massone C, Hofmann-Wellenhof R, Ahlgren-Siess V, Gabler G, Ebner C, Soyer HP. Melanoma screening with cellular phones. *PLoS One.* 2007;2:e483.
34. Kroemer S, Fruhauf J, Campbell TM, et al. Mobile teledermatology for skin tumour screening: diagnostic accuracy of clinical and dermoscopic image tele-evaluation using cellular phones. *Br J Dermatol.* 2011;164:973-979.
35. Borre A, Terstappen K, Sandberg C, Paoli J. Mobile teledermoscopy-there's an app for that!. *Dermatol Pract Concept.* 2013;3:41-48.
36. Janda M, Loescher LJ, Soyer HP. Enhanced skin self-examination: a novel approach to skin cancer monitoring and follow-up. *JAMA Dermatol.* 2013;149:231-236.
37. Janda M, Loescher LJ, Banan P, Horsham C, Soyer HP. Lesion selection by melanoma high-risk consumers during skin self-examination using mobile teledermoscopy. *JAMA Dermatol.* 2014;150:656-658.
38. Viola KV, Tolpinrud WL, Gross CP, Kirsner RS, Imaeda S, Federman DG. Outcomes of referral to dermatology for suspicious lesions: implications for teledermatology. *Arch Dermatol.* 2011;147:556-560.
39. US Food and Drug Administration website. FDA outlines oversight of mobile medical applications. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm263340.htm>. Accessed March 17, 2015.
40. US Food and Drug Administration website. FDA Safety and Innovation Act. Available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm20027187.htm>. Accessed March 17, 2015.
41. US Food and Drug Administration website. Mobile medical applications. Available at: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ConnectedHealth/MobileMedicalApplications/default.htm>. Accessed March 17, 2015.
42. Claridge E, Cotton S, Hall P, Moncrieff M. From colour to tissue histology: physics-based interpretation of images of pigmented skin lesions. *Med Image Anal.* 2003;7:489-502.
43. Matts PJ, Dykes PJ, Marks R. The distribution of melanin in skin determined in vivo. *Br J Dermatol.* 2007;156:620-628.
44. Terstappen K, Suurküla M, Hallberg H, Ericson MB, Wennberg AM. Poor correlation between spectrophotometric intracutaneous analysis and histopathology in melanoma and nonmelanoma lesions. *J Biomed Opt.* 2013;18:061223.
45. Moncrieff M, Cotton S, Claridge E, Hall P. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions. *Br J Dermatol.* 2002;146:448-457.
46. Govindan K, Smith J, Knowles L, Harvey A, Townsend P, Kenealy J. Assessment of nurse-led screening of pigmented lesions using SIAscope. *J Plast Reconstr Aesthet Surg.* 2007;60:639-645.
47. Haniffa MA, Lloyd JJ, Lawrence CM. The use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma in the setting of a melanoma screening clinic. *Br J Dermatol.* 2007;156:1350-1352.
48. Glud M, Gniadecki R, Drzewiecki KT. Spectrophotometric intracutaneous analysis versus dermoscopy for the diagnosis of pigmented skin lesions: prospective, double-blind study in a secondary reference centre. *Melanoma Res.* 2009;19:176-179.
49. Tomatis S, Carrara M, Bono A, et al. Automated melanoma detection with a novel multispectral imaging system: results of a prospective study. *Phys Med Biol.* 2005;50:1675-1687.
50. Carrara M, Bono A, Bartoli C, et al. Multispectral imaging and artificial neural network: mimicking the management decision of the clinician facing pigmented skin lesions. *Phys Med Biol.* 2007;52:2599-2613.
51. Hall PN, Hunter JE, Walter FM, Norris P. Use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma. *Br J Dermatol.* 2008;158:420-421.
52. Emery JD, Hunter J, Hall PN, Watson AJ, Moncrieff M, Walter FM. Accuracy of SIAscope for pigmented skin lesions encountered in primary care: development and validation of a new diagnostic algorithm. *BMC Dermatol.* 2010;10:9.
53. Wood A, Morris H, Emery J, et al. Evaluation of the MoleMate training program for assessment of suspicious pigmented lesions in primary care. *Inform Prim Care.* 2008;16:41-50.
54. Watson T, Walter FM, Wood A, et al. Learning a novel technique to identify possible melanomas: are Australian general practitioners better than their U.K. colleagues? *Asia Pac Fam Med.* 2009;8:3.
55. Walter FM, Morris HC, Humphrys E, et al. Effect of adding a diagnostic aid to best practice to manage suspicious pigmented lesions in primary care: randomised controlled trial. *BMJ.* 2012;345:e4110.
56. Gutkowicz-Krusin D, Elbaum M, Jacobs A, et al. Precision of automatic measurements of pigmented skin lesion parameters with a MelaFind(TM) multispectral digital dermoscope. *Melanoma Res.* 2000;10:563-570.

57. Elbaum M, Kopf AW, Rabinovitz HS, et al. Automatic differentiation of melanoma from melanocytic nevi with multispectral digital dermoscopy: a feasibility study. *J Am Acad Dermatol.* 2001;44:207-218.
58. Friedman RJ, Gutkowicz-Krusin D, Farber MJ, et al. The diagnostic performance of expert dermatoscopists vs a computer-vision system on small-diameter melanomas. *Arch Dermatol.* 2008;144:476-482.
59. Monheit G, Cognetta AB, Ferris L, et al. The performance of MelaFind: a prospective multicenter study. *Arch Dermatol.* 2011;147:188-194.
60. Wells R, Gutkowicz-Krusin D, Veledar E, Toledano A, Chen SC. Comparison of diagnostic and management sensitivity to melanoma between dermatologists and MelaFind: a pilot study. *Arch Dermatol.* 2012;148:1083-1084.
61. Cukras AR. On the comparison of diagnosis and management of melanoma between dermatologists and MelaFind. *JAMA Dermatol.* 2013;149:622-623.
62. Rigel DS, Roy M, Yoo J, Cockerell CJ, Robinson JK, White R. Impact of guidance from a computer-aided multispectral digital skin lesion analysis device on decision to biopsy lesions clinically suggestive of melanoma. *Arch Dermatol.* 2012;148:541-543.
63. Hauschild A, Chen SC, Weichenthal M, et al. To excise or not: impact of MelaFind on German dermatologists' decisions to biopsy atypical lesions. *J Dtsch Dermatol Ges.* 2014;12: 606-614.
64. Singer N. Dissent over a device to help find melanoma. *The New York Times.* March 20, 2013.
65. 2013 MELA Sciences physician user lease agreement.
66. Morimoto T, Kimura S, Konishi Y, et al. A study of the electrical bio-impedance of tumors. *J Invest Surg.* 1993;6:25-32.
67. Piperno G, Frei EH, Moshitzky M. Breast cancer screening by impedance measurements. *Front Med Biol Eng.* 1990;2: 111-117.
68. Glickman YA, Filo O, David M, et al. Electrical impedance scanning: a new approach to skin cancer diagnosis. *Skin Res Technol.* 2003;9:262-268.
69. Har-Shai Y, Glickman YA, Siller G, et al. Electrical impedance scanning for melanoma diagnosis: a validation study. *Plast Reconstr Surg.* 2005;116:782-790.
70. Aberg P, Nicander I, Hansson J, Geladi P, Holmgren U, Ollmar S. Skin cancer identification using multifrequency electrical impedance—a potential screening tool. *IEEE Trans Biomed Eng.* 2004;51:2097-2102.
71. Aberg P, Geladi P, Nicander I, Hansson J, Holmgren U, Ollmar S. Non-invasive and microinvasive electrical impedance spectra of skin cancer - a comparison between two techniques. *Skin Res Technol.* 2005;11:281-286.
72. Aberg P, Birgersson U, Elsner P, Mohr P, Ollmar S. Electrical impedance spectroscopy and the diagnostic accuracy for malignant melanoma. *Exp Dermatol.* 2011;20:648-652.
73. Mohr P, Birgersson U, Berking C, et al. Electrical impedance spectroscopy as a potential adjunct diagnostic tool for cutaneous melanoma. *Skin Res Technol.* 2013;19:75-83.
74. Malvehy J, Hauschild A, Curiel-Lewandrowski C, et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multi-centre, prospective and blinded clinical trial on efficacy and safety. *Br J Dermatol.* 2014;171:1099-1107.

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Practical application of new technologies for melanoma diagnosis

Part II. Molecular approaches

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Learning objectives

After completing this learning activity participants should be able to identify new biopsy technologies that may facilitate melanoma diagnosis; explain the advantages and disadvantages of each new biopsy technology and how it could impact their patient population; and recognize the molecular techniques that may help them develop an optimal and personalized treatment plan for patients who may have melanoma.

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The criterion standard for diagnosing cutaneous melanoma continues to be histologic examination. However, classifying some melanocytic lesions by conventional microscopy can be problematic if they exhibit some architectural or morphologic characteristics of both nevus and melanoma. Moreover, histologic appearance does not always predict biologic behavior. There is therefore a need and opportunity to develop new technologies that can facilitate the histologic diagnosis of melanoma and potentially help distinguish lesions with a lesser or greater risk of metastasis. In part II of this 2-part continuing medical education article, we will review the molecular technologies currently available for facilitating melanoma diagnosis, including comparative genomic hybridization, fluorescence in situ hybridization, and epidermal genetic retrieval. Our goal is to provide the clinician with an up to date understanding of these molecular approaches so that they can be applied to their management of challenging melanocytic lesions. (J Am Acad Dermatol 2015;72:943-58.)

Key words: fluorescence; genomic; hybridization; melanoma; molecular; nevus.

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OPPORTUNITY TO IMPROVE MELANOMA DIAGNOSTIC EFFICIENCY AND MANAGEMENT IN THE MOLECULAR ERA

Key points

- Some melanocytic lesions may be difficult to diagnose histologically
- Histologic features may not predict biologic behavior
- Molecular technologies may facilitate melanoma diagnosis and provide prognostic information
- Validation of molecular tests is required before clinical implementation

While the general microscopic features of melanoma and nevi are well described, some lesions will exhibit ≥ 1 feature(s) of both, making it difficult to render a definitive histologic diagnosis. Individual dermatopathologists may weigh particular histologic characteristics differently, which may contribute to the poor interobserver diagnostic concordance reported in some studies.¹⁻⁴ Differentiating lesions with spitzoid histology is particularly problematic.⁵ Lesions displaying severely dysplastic and/or atypical features, or in which melanoma may be arising from a nevus precursor, present a particular quandary because management varies according to the diagnosis—nevi can usually be observed, but melanomas require definitive reexcision and, in some cases, obtaining a biopsy specimen from a sentinel lymph node for staging.^{6,7}

Some histologic features in melanoma can be predictive of biologic behavior, such as the presence of ulceration and mitotic figures, which correlate with risk of metastasis and poorer survival.⁸ On the other hand, approximately 5% to 10% of patients with minimally invasive melanoma (ie, a Breslow depth of <1 mm) lacking these features will ultimately develop metastatic disease.⁹ If such lesions that go on to display more aggressive behavior could be identified at the time that a biopsy specimen is obtained, these patients could be offered sentinel lymph node biopsy for more accurate staging or adjuvant therapy, which would not be appropriate for all patients with histologically apparent low-risk lesions. In the molecular era, there is precedent for analyzing genetic markers or patterns of gene expression (ie, gene signatures) in cancer to gain diagnostic or prognostic information that cannot be gleaned from histologic examination alone. For example, expression levels of a panel of genes have been used in breast cancer to predict which patients with histologically equivalent disease have increased risk of recurrence or metastasis.¹⁰

Similar molecular tests have been designed to distinguish between nevus and melanoma and to provide information regarding melanoma prognosis. In this review, we will discuss several technologies and the clinical scenarios in which they have been applied to facilitate melanoma diagnosis and/or provide prognostic information.

COMPARATIVE GENOMIC HYBRIDIZATION

Principles, methods, and pitfalls

Key points

- Comparative genomic hybridization can be performed on formalin-fixed, paraffin-embedded tissues
- Genome-wide DNA differences between test and reference samples are detected
- Comparative genomic hybridization may reveal chromosomal alterations in cancerous lesions
- False-negative results occur if tumor cells are not adequately represented in sample
- Comparative genomic hybridization is unable to detect point mutations and balanced translocations
- Array-based comparative genomic hybridization is more sensitive than traditional comparative genomic hybridization

In 1992, Kallioniemi et al¹¹ developed comparative genomic hybridization (CGH) to expedite the identification and mapping of genome-wide DNA copy number alterations. Deviations from normal copy numbers can be applied to cancer research by enabling the identification of genetic aberrations that occur in cancers. For instance, the loss of tumor suppressor genes or amplification of oncogenes can be identified by comparing DNA from normal tissue to that from tumors. In traditional CGH, DNA from tumor and reference (control) samples are differentially labeled with fluorochromes and simultaneously hybridized to normal metaphase chromosomes (Fig 1, A). The marked DNA competes for binding locations; under microscopic examination, fluorescent areas of disproportionate binding indicate gene amplification or deletion. CGH can be performed on formalin-fixed, paraffin-embedded tissues, enabling retrospective analysis. The resolution of traditional CGH is limited primarily by the use of metaphase chromosomes, which prevents detection of alterations involving small DNA segments (<20 Mb) or those situated near sites containing other genomic aberrations.

In 1998, Pinkel et al¹² reported the development of an array-based CGH method to overcome some of

Abbreviations used:

- CGH: comparative genomic hybridization
EGIR: epidermal genetic information retrieval
FISH: fluorescence in situ hybridization

the limitations of traditional CGH. In array-based CGH, the tumor and reference samples are hybridized to an array of thousands or hundreds of thousands of DNA sequences instead of metaphase chromosomes (Fig 1, B). The genomic resolution is determined by the map distance between the DNA targets or by the length of the cloned DNA segments, but generally permits the detection of much smaller or focal alterations to provide much higher resolution than traditional CGH. In addition, array-based CGH is technically easier to perform than traditional CGH. Both CGH methods, however, require a relatively large or pure tumor sample for successful analysis because genomic alterations in the tumor could be missed if the sample is too small or contaminated by nontumor cells. Other potential limitations of these methods are an inability to detect point mutations and balanced rearrangements because of restrictions in resolution and the lack of discernible preference in hybridization to large DNA segments.

Comparative genomic hybridization analyses of melanoma

Key points

- Bastian et al pioneered the application of comparative genomic hybridization to melanoma
- Common aberrations in melanoma are loss of 9q and 10, and gains in 7
- Distinct genomic patterns are associated with particular melanoma subtypes
- Regions containing oncogenes (BRAF and MITF) are frequently amplified, while regions containing tumor suppressor genes (CDKN2A and PTEN) are frequently deleted

Before CGH, cytogenetic analysis by karyotyping was used in the 1980s to identify abnormalities in chromosomes 1, 6, 7, and 9 that were present in melanomas compared to nevi.¹³⁻¹⁵ Most of the early work examining melanoma by CGH was reported by Bastian et al.¹⁶ In an early study,¹⁶ they analyzed manually dissected tumor sections from 32 primary melanomas. Losses occurred on chromosomes 9 (81%; mostly p arm), 10 (63%), 6q (28%), and 8p (22%). Gains involved chromosomes 7 (50%), 8 (34%), 6p (28%), 1q (25%), 20 (13%), 17 (13%),

and 2 (13%). Amplifications were seen at 4q12, 5p14.3-pter, 7q33-qter, 8q12-13, 11q13.3-14.2, and 17q25. An analysis of copy number changes among the spectrum of lesions indicated that losses of 9 and 10 occur early in melanoma progression, whereas gains of 7 occur later. This sequence of events was further substantiated by an intratumoral comparison of copy number changes in areas with radial and vertical growth phase patterns. There are also case reports in which CGH was used to show molecular heterogeneity within individual melanoma tumors.^{17,18} In a subsequent study by Bastian et al,¹⁹ acral melanomas revealed significantly greater genomic amplification compared to superficial spreading melanomas. The most frequently amplified regions in acral melanomas were 11q13 (47%), 22q11-13 (40%), and 5p15 (20%). In addition, isolated melanocytes with amplifications in the epidermis ≤ 3 mm beyond the histologically recognizable extent of the melanomas were found in 5 of 15 invasive acral melanomas. Namiki et al²⁰ performed CGH on 20 primary cutaneous melanomas obtained by laser capture or manual microdissection. There were no differences in the average number of aberrations between acral and nonacral melanoma tumors, although gains of 5q and 11q13 were more frequent and 10q loss was less frequent in acral melanomas.

Expanding on an earlier study,²¹ Curtin et al²² used CGH to analyze genome-wide alterations and determined mutational status of BRAF and NRAS in 126 melanomas and found distinct patterns associated with melanomas from skin with chronic sun-induced damage, skin without such damage, and from acral and mucosal sites. Melanoma samples could be correctly classified into the 4 groups with 70% accuracy. While 81% of melanomas with genomic changes associated with skin without chronic sun damage had mutations in BRAF or NRAS, other genomic changes seen in the majority of melanomas from the other groups had mutations in neither gene.

Gast et al²³ reported on particular oncogenes and tumor suppressor genes that were targets of amplifications and deletions. Lazar et al²⁴ used CGH to assess differences between BRAF- and NRAS-mutated primary melanomas in a set of 47 tumors. BRAF-mutant melanomas exhibited more frequent losses of 10q23-q26 and gains of 7 and 1q23-q25, while loss of 11q23-q25 was found mainly in conjunction with NRAS mutation. Primary melanomas without BRAF or NRAS mutations showed frequent alterations in chromosomes 17 and 4.

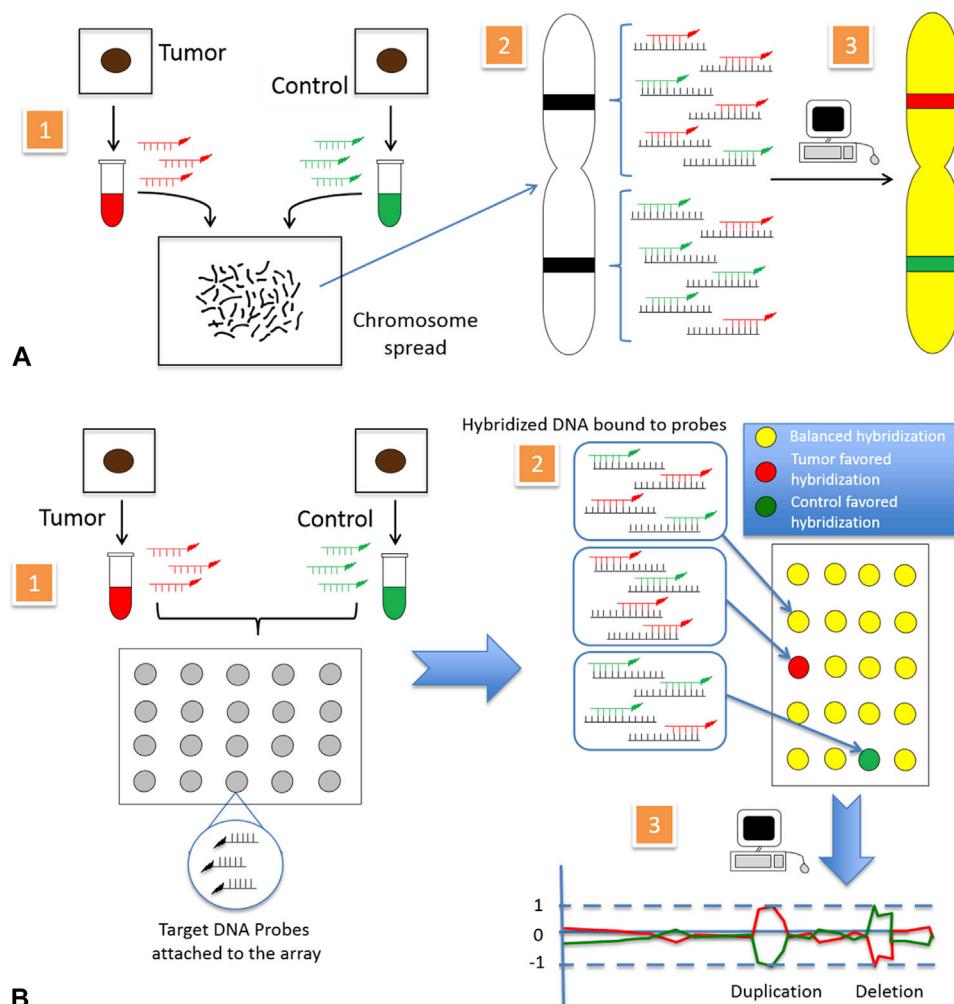


Fig 1. Comparative genomic hybridization (CGH). **A**, Traditional CGH. (1) DNA from tumor (either formalin-fixed paraffin-embedded or fresh tissue) and reference samples (ie, control nontumor tissue) are differentially labeled with fluorochromes and simultaneously hybridized to normal metaphase chromosomes. (2) During hybridization, the tumor and reference DNA sequences compete for shared target sequences on the metaphase spread. (3) The binding ratio between the tumor and reference DNA at a given chromosomal locus can be quantified by fluorescence intensities and is approximately proportional to the ratio of the copy numbers in their respective genomes. Alterations in the intensity ratio of the fluorochromes within the metaphase spread indicate quantitative differences between the tumor and reference genomes. **B**, Array-based CGH. (1) DNA from tumor and reference samples are differentially labeled with fluorochromes and simultaneously hybridized to DNA probes on the microarray where they compete for shared target sequences. (2) Alterations in the intensity ratio of the fluorochromes indicate quantitative differences between the tumor and reference genomes. (3) A computer analyzes the scanned array and determines the ratio of the copy numbers to generate a plot. A gain in signal intensity of the tumor-labeled DNA indicates a duplication; a loss in intensity indicates a deletion.

Comparative genomic hybridization analyses of nevi

Key points

- Compared to melanoma, most nevi lack or have isolated genomic aberrations
- Spitz nevi typically exhibit gains in chromosome 11p, not seen in melanoma

- No significant correlations have been found between blue nevi and melanoma risk
- Congenital and deep penetrating nevi exhibit genomic profiles that may be distinguished from melanoma
- Long-term patient follow-up is needed to establish clinical and molecular correlations

Several studies have applied CGH to distinguish melanoma from melanocytic nevi. Bastian et al²⁵ used CGH to analyze DNA from 17 Spitz nevi. No chromosomal aberrations were seen in 13 lesions. A gain of 11p was seen in 3 lesions, and a gain of 7q21 was seen in 1 lesion. In a more comprehensive study, this group applied CGH to a panel of 186 melanocytic tumors (132 melanomas and 54 nevi).²¹ Whereas 96% of melanomas had some form of chromosomal aberration, this was seen in only 13% of the nevi; all were Spitz nevi that had an isolated gain of 11p. This particular aberration was not seen in any of the melanomas. Harvell et al²⁶ similarly used CGH to analyze a small panel of Spitz nevi and melanomas. Two of 3 Spitz nevi had no significant chromosomal alterations, while the third showed a gain of 11p. By contrast, 2 melanomas had multiple copy number alterations, including amplification of 1q and deletion of 9. Harris et al²⁷ reported a patient with multiple lesions that histologically could not be differentiated as melanomas or pagetoid Spitz nevi. Analysis of the tumors by CGH did not reveal any common driver mutations or chromosomal anomalies, suggesting that the patient had multiple pagetoid Spitz nevi (rather than melanomas).

Held et al²⁸ used CGH to classify and distinguish blue nevi from melanoma. Twenty-three dermal melanocytic tumors that were initially diagnosed as benign or ambiguous were evaluated. Nine of 23 patients had chromosomal aberrations, including 3 patients with tumor recurrence or progression. North et al²⁹ and Held et al³⁰ described cases of "blue nevi" with chromosomal aberrations that behaved like melanoma.

Bastian et al³¹ analyzed chromosomal aberrations in different types of proliferations arising in congenital nevi. Cases were assigned to 6 groups according to the following histologic patterns: without atypical features (group I, n = 6), with foci of increased cellularity (group II, n = 4), with a proliferation simulating superficial spreading melanoma *in situ* (group III, n = 3), with a proliferation simulating nodular melanoma (group IV, n = 9), proliferating neurocristic hamartoma (group V, n = 1), and melanoma arising in congenital nevus (group VI, n = 6). No aberrations were found in groups I, II, or III. On the other hand, aberrations of whole chromosomes exclusively were seen in most cases of groups IV and V, which differed significantly from the varied aberrations found in group VI and melanomas that were independent of congenital nevi. It was postulated that these differences in aberration patterns found in congenital nevi might explain their more benign

clinical behavior. Similarly, Nguyen et al³² reported a case of a congenital nevus with a proliferative nodule that did not contain any chromosomal abnormalities.

Magro et al³³ applied CGH analysis to 6 deep penetrating nevi, and all 6 tumors had normal cytogenetic profiles. In 1 case that progressed to overt melanoma, conversion to an abnormal cytogenetic profile was demonstrated. Su et al³⁴ described 2 cases of newborns with scalp lesions that grew quickly, and CGH analysis revealed multiple chromosomal aberrations in both lesions that ultimately metastasized.

Using comparative genomic hybridization to predict melanoma prognosis

Key points

- Degree of chromosomal instability may correlate with poor outcome
- Homozygous deletions may be more specific predictors of poor outcome

In the study by Namiki et al²⁰ described above, an attempt was made to associate CGH findings in primary tumors with patient outcome. While they found that the number of genomic aberrations did not appear to vary with tumor depth, gains in 6p were seen only in the thickest tumors. Patients with 6p or 1q gains had a lower overall survival rate. Hirsch et al³⁵ used CGH to study 20 melanomas with a range of clinical outcomes. They compared lesions from 10 patients who died a median of 3.7 years after diagnosis with 10 patients who had a median disease-free survival of 14.8 years. They found an association between the degree of chromosomal instability and poor survival. While melanomas with good outcome showed only a few chromosomal imbalances (mean, 1.6 alterations per case), melanomas with poor outcome had significantly more chromosomal aberrations (13.9 per case).

Boi et al³⁶ also used CGH to evaluate 31 melanomas (all >1.5 mm in depth) with outcomes data. Although a variety of highly recurrent genomic lesions were identified, the total number of copy number alterations per tumor was not a discriminator of clinical outcome. In addition, validation of these CGH results by quantitative polymerase chain reaction studies on an extended population of 65 melanoma samples confirmed the absence of predictive value for the most recurrent alterations. Instead, their analysis revealed specific prognostic potential of the frequency of homozygous deletions (representing <3% of the total aberrations per sample), which was strongly associated with sentinel

lymph node positivity, distant metastasis, and poor patient survival.

Obtaining comparative genomic hybridization analysis

Key points

- Comparative genomic hybridization testing is available through several academic laboratories
- Insurance coverage for comparative genomic hybridization is variable

CGH testing can be obtained through several academic facilities. These include the University of California San Francisco (\$1800 plus \$275 for slide consultation, turnaround time 3 weeks) and the University of California Los Angeles (\$860, turnaround time 3 weeks), among others (personal communications, March 2015).

There are no specific *Current Procedural Terminology* codes for CGH/melanoma (falls under 81479, unlisted molecular procedure code),³⁷ and obtaining insurance coverage can be difficult. For example, Aetna considers CGH testing for melanoma experimental and investigational because of “insufficient evidence of effectiveness.”³⁸ Anthem takes a similar position and considers CGH testing for melanoma “not medically necessary.”³⁹

FLUORESCENCE IN SITU HYBRIDIZATION

Principles, methods, and pitfalls

Key points

- Fluorescence in situ hybridization uses fluorescent probes to bind specific DNA segments in nuclei of cells
- It can be performed on sections of formalin-fixed, paraffin-embedded tissues
- Fluorescence in situ hybridization can only detect genes and chromosomes targeted by specific probes, which may detect balanced chromosomal translocations and single-point mutations
- The technical expertise required for fluorescence in situ hybridization is considerably less than that for comparative genomic hybridization

Fluorescence in situ hybridization (FISH) is a molecular cytogenetic method for determining the copy number of specific regions or sequences of DNA (reviewed by Gerami and Zembowicz⁴⁰). Short strands of fluorescently labeled DNA (ie, probes) are used to label complementary target sequences in a given tissue sample (Fig 2). Unlike CGH, FISH can detect balanced chromosomal translocations and

single-point mutations; however, the probes limit detection to prespecified DNA sequences. In addition, only a finite number of probes (usually 4) can be used simultaneously on a given sample; each probe must be tagged with a distinct fluorochrome that emits wavelengths of light that do not overlap with those emitted from the other fluorochromes. Probes are usually hybridized to 5-mm thick sections of formalin-fixed and paraffin-embedded tissues; after any unbound probes are washed away, the tissue section (or even individual cells) can be examined by fluorescence microscopy.

Hybridization of a single probe indicates the presence (and location) of a specific DNA target sequence in the cell and would generate 1 fluorescent dot that could be visualized. Ideally, every diploid cell containing the specific target sequence should undergo hybridization with 2 probe molecules and generate 2 fluorescent dots. The presence of >2 dots in a cell would indicate gain or amplification of the specific DNA sequence. Conversely, <2 dots (ie, 1 or 0) in a cell would indicate loss or deletion of the DNA sequence. The copy number of the specific DNA sequence can then be determined from the percentage of nuclei containing >2 copies or from the percentage of cells demonstrating an increase or loss of signal compared to a probe directed against a chromosomal centromere.

Early fluorescence in situ hybridization studies of melanoma utilizing 4 probes

Key points

- Fluorescence in situ hybridization targets were based on chromosomal aberrations discovered through comparative genomic hybridization
- Four-probe assay developed targeting genes on 6p25, 6q23, 11q13, and centromere 6
- Most melanomas demonstrate copy number increases of 11q and 6p, and can be easily distinguished from common nevi
- Polyploidy can lead to false-positive fluorescence in situ hybridization results

Although FISH is an older technology than CGH, its application to melanocytic lesions came later; data from CGH-based studies described above were used to develop probes for FISH. A summary of the genetic aberrations commonly found in melanomas from CGH and FISH studies is presented in Table I. Much of the early work using FISH in melanoma was performed by Gerami et al,⁴⁰ who assembled panels of probes based on known DNA copy number alterations of chromosomes 6 and 11 in melanoma.

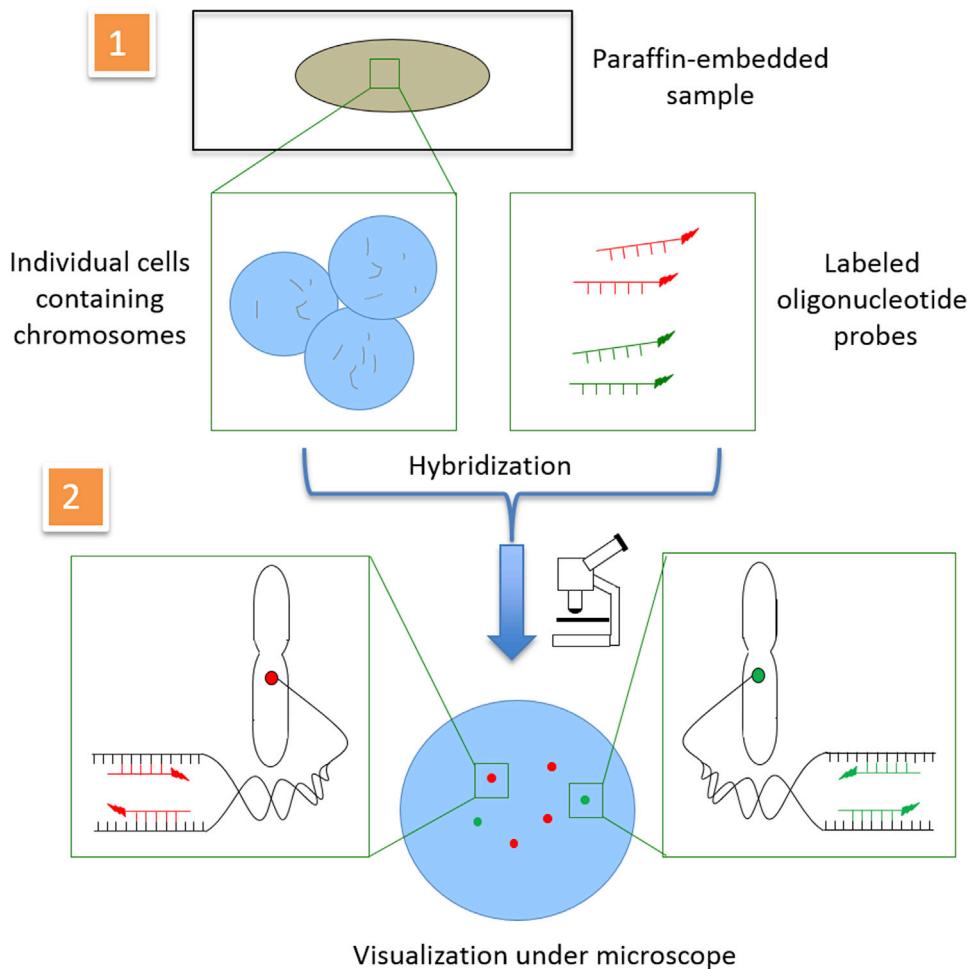


Fig 2. Fluorescence in situ hybridization (FISH). (1) Short strands of fluorescently labeled DNA (ie, probes) are used to label complementary target sequences in a given tissue sample. Probes are usually hybridized to 5-mm thick sections of formalin-fixed and paraffin-embedded tissues; after any unbound probes are washed away, the tissue section (or even individual cells) can be examined by fluorescence microscopy. (2) Hybridization of a single probe indicates the presence (and location) of a specific DNA target sequence in the cell and would generate 1 fluorescent dot that could be visualized. Ideally, every diploid cell containing the specific target sequence should undergo hybridization with 2 probe molecules and generate 2 fluorescent dots. The presence of >2 dots in a cell would indicate a gain or amplification of the specific DNA sequence. Conversely, <2 dots (ie, 1 or 0) in a cell would indicate a loss or deletion of the DNA sequence.

These probes were applied to a training set of 301 tumors, and then validated on an independent set of 169 histologically unequivocal nevi and melanomas and 27 ambiguous lesions for which clinical follow-up was available.⁴¹ A combination of 4 probes targeting genes on 6p25 (RREB1), 6q23 (MYB), 11q13 (CCND1), and centromere 6 (Cep6) provided the highest diagnostic discrimination, with most melanomas showing copy number increases of 11q and 6p. The assay correctly classified melanoma with 87% sensitivity and 95% specificity, and also identified as melanoma 6 of 6 cases with ambiguous pathology that later metastasized. Similarly, Morey

et al⁴² used the same approach to evaluate 40 unequivocal melanocytic tumors (10 metastatic melanomas, 10 primary melanomas, and 20 melanocytic nevi). The FISH assay distinguished the melanomas and the nevi with a sensitivity of 90% and a specificity of 95%. Gerami et al⁴³ subsequently evaluated 110 patients with nevi and 123 patients with melanoma (70 superficial spreading, 28 lentigo maligna, 22 nodular, and 3 acral lentiginous types). The assay achieved an overall sensitivity of 83% and specificity of 94%. The 6p25 gain criterion had the highest sensitivity overall and in each subtype. The assay was most

Table I. Chromosomal alterations in malignant melanoma

Chromosome locus	Associated gene	Gain (+) or loss (-)	Other
6p25	RREB1	+	4-probe FISH assay, poor prognosis
6q23	MYB	+/-	4-probe FISH assay
11q13	CCND1	+	4-probe FISH assay
Centromere 6	CEP6*		4-probe FISH assay
8q24	MYC	+	Aggressive melanoma, amelanotic melanoma
10q23	BRAF	-	
7	BRAF	+	
1q23	BRAF	+	
11q13	NRAS	-	Acral melanoma, poor prognosis
12q13	CDK4	-	
9p21	CDKN2A (p16)	-	
Chromosome 10	PTEN and BRAF	-	
11p		+	Spitz nevi, not melanoma

*Used to compare gains and losses on chromosome 6.

sensitive in the subgroups of nodular and acral melanomas and least sensitive in the superficial spreading subtype. Abasolo et al⁴⁴ used the 4-probe assay to evaluate 50 melanocytic skin lesions (including 31 melanomas and 10 nevi). Nevi and melanomas were distinguished with a sensitivity of 100% and a specificity of 94%, with the most sensitive criterion being a gain in 6p25 seen in all the melanomas.

It is important to note that the presence of tetraploidy in nevi can cause a false-positive FISH result. Zembowicz et al⁴⁵ prospectively analyzed 140 lesions, and found that 27% of abnormal FISH results were false-positive results because of tetraploidy. After correcting for known false-positive results, all lesions considered atypical nevi had normal FISH signals. Abnormal FISH signals were reported in 30% of lesions considered histologically borderline and in 48% of lesions in which a diagnosis of melanoma was favored. Finally, Fang et al⁴⁶ analyzed results of a previous study to highlight the limitations FISH based on the 4-probe assay. Of 50 melanocytic nevi, 49 were negative after correction for tetraploidy (98% specificity). Of 50 primary melanomas, 41 were FISH-positive (82% sensitivity). Of the 9 FISH-negative melanomas, 6 metastasized. Therefore, a rare nevus may be FISH-positive, and some primary metastasizing melanomas and even metastatic melanomas may be FISH-negative.

Applications of the 4-probe fluorescence in situ hybridization assay

Key points

- In addition to distinguishing benign and malignant melanocytes, fluorescence in situ hybridization assays may have utility in melanoma microstaging, and in

differentiating epithelioid blue nevus from blue nevus-like melanoma

- Fluorescence in situ hybridization may discriminate between spitzoid melanomas and Spitz nevi
- A fraction of dysplastic nevi are fluorescence in situ hybridization-positive

Similar to CGH, FISH assays may be useful in distinguishing histologically ambiguous melanocytes as malignant or benign. Moore and Gasparini⁴⁷ used the 4-probe assay to analyze a cohort of 500 samples including 157 common nevi, 176 dysplastic nevi, and 167 melanomas. They identified genetic abnormalities in 84% of melanomas and 2% of nevi without atypia, while genetic abnormalities were respectively identified in 6.3%, 6.7%, and 10.3% of nevi identified with mild, moderate, and severe atypia.

Martin et al⁴⁸ applied the 4-probe assay to 51 patients with Spitz nevi and long-term median follow-up (8.2 years). Control groups included 11 nevi and 14 melanomas. While Spitz nevi from 32 (63%) patients did not show cytogenetic abnormalities, those from 19 (37%) patients were positive. Spitz nevi with a positive FISH profile revealed chromosome X polysomy in 14 of 18 (78%) patients. All melanomas had a positive FISH profile, and 4 of 11 (36%) had chromosome X polysomy. No differences in histology were detected between Spitz nevi with and without genetic abnormalities.

Raskin et al⁴⁹ used array CGH and the 4-probe assay to evaluate 16 atypical Spitz tumors (8 associated with a positive sentinel lymph node, 1 with distant metastasis), 8 Spitz nevi, and 2 spitzoid melanomas. The CGH analysis revealed chromosomal aberrations in 7 of 16 atypical Spitz lesions and

both spitzoid melanomas. The Spitz tumor with metastasis lacked the aberrations in 6 and 11q targeted by FISH probes. The FISH assay also failed to detect 1 spitzoid melanoma, and the other chromosomally aberrant atypical Spitz tumors. Finally, Requena et al⁵⁰ used the 4-probe assay to evaluate 12 spitzoid melanomas and 6 Spitz nevi. Chromosomal aberrations were detected in 7 of the 8 spitzoid melanomas and in none of the 5 Spitz nevi, yielding a sensitivity of 88% and specificity of 100% in distinguishing between Spitz nevi and spitzoid melanoma.

Another potential application of FISH includes differentiating melanoma cells from nevoid cells to determine the precise tumor depth for staging of melanomas harboring both cell types. In a study by Newman et al,⁵¹ 28 of 36 cases (78%) of melanoma were marked by FISH probes in areas of apparent histologic malignancy while the nevus components were uniformly negative. The demarcation of malignant cells by FISH suggests that tumor depth can be determined with greater accuracy and therefore could affect both staging and management. The same group also analyzed epithelioid blue nevi and blue nevus-like cutaneous melanoma metastases.⁵² Twenty lesions were examined, with 9 of 10 malignant lesions staining positive; all 10 blue nevi were negative. They also applied this assay to evaluate 10 nevoid melanomas (4 of which had metastasized) and 10 mitotically active nevi.⁵³ While all 10 nevoid melanomas showed copy number abnormalities, none were present in the 10 mitotically active nevi.

FISH may also be useful in differentiating histopathologically ambiguous deposits of melanocytes found in lymph nodes. Dalton et al⁵⁴ used the 4-probe assay to distinguish intranodal nevi from metastatic melanoma in 59 samples from 41 patients. Of 24 lesions of metastatic melanoma, 20 (83%) were positive, while 3 of the 4 negative samples were unequivocal melanoma metastases and 1 was equivocal. All but 1 of 17 (6%) nodal nevi revealed no chromosomal aberrations by FISH.

Commercialization of the fluorescence in situ hybridization assay

Key points

- Original fluorescence in situ hybridization assay commercialized by Abbott
- In the United States, the Abbott assay is licensed to NeoGenomics Laboratories
- Dermatologists can refer cases to NeoGenomics or to tertiary care centers
- Fluorescence in situ hybridization testing is often covered by insurance

The original FISH assay was patented and commercialized by Abbott (Abbott Molecular, Abbott Park, IL) and is exclusively licensed to NeoGenomics Laboratories (Fort Myers, FL).⁵⁵ They provide the technical component and have developed an innovative service (MelanoSITE) allowing pathologists to interpret FISH results using a dedicated Internet portal. In the United States, this assay is largely performed at the academic centers involved in the development of the test and as a commercial service by NeoGenomics Laboratories (Neo-SITE Melanoma; cost approximately \$1350; personal communication, March 2015). A melanoma FISH test is also available through Miraca Life Sciences. Outside of the United States, Abbott Molecular's assay is available as a diagnostic kit.

One of the largest referral centers for FISH testing is at the University of California, San Francisco, where North et al⁵⁶ recently reported their experience in 804 ambiguous melanocytic lesions, of which 88% received a more definitive benign or malignant final diagnosis based on FISH results. Most referred lesions were Spitz tumors (47%), followed by combined nevi (9%), acral or mucosal nevi (9%), dysplastic nevi (7%), and blue or deep penetrating nevi (6%). Of the 630 cases that were FISH-negative, the final diagnosis was benign in 489 (78%) cases, ambiguous in 91 cases (14%), and malignant in 50 cases (8%). Of 124 cases that were FISH-positive, 117 (94%) had a final diagnosis of melanoma, 1 case had an equivocal final diagnosis, and 6 were interpreted, despite the positive FISH result, as melanocytic nevi. The cost for referrals is \$1500, not including pathological review, with a turnaround time of approximately 2 weeks (personal communication, March 2015). Other academic referral centers for FISH testing include the Mayo Clinic and the Cleveland Clinic.

FISH testing for melanoma is more likely to be covered by insurance than CGH. There are several *Current Procedural Terminology* codes for FISH that distinguish whether the analysis is manual or by computer, and are usually billed separately for each probe used.³⁷

Fluorescence in situ hybridization assays using alternate probe sets and algorithms

Key points

- Early studies revealed limitations of the 4-probe set
- New probe sets have enhanced sensitivity and specificity
- Combining algorithms does not significantly increase diagnostic performance

Several reviews and commentaries have highlighted the limitations of FISH analysis using the original 4-probe set.^{55,57,58} Additional and/or alternate probe sets were developed to enhance both sensitivity and specificity. Hossain et al⁵⁹ used 4 probes targeting chromosomes 6, 7, 11, and 20 to evaluate 32 nevi and 31 melanomas. Chromosomal anomalies were found in 2 (6%) nevi and 29 (94%) melanomas, for an overall sensitivity of 94% and specificity of 94%. Gammon et al⁶⁰ coupled a 2-probe assay targeting 9p21 and Cep9 with the original 4-probe assay to evaluate 43 unequivocal spitzoid melanomas. While the 4-probe assay demonstrated 70% sensitivity, the 2 assays together achieved a combined sensitivity of 85%. Gerami et al⁶¹ used an alternative 4-probe assay (targeting 9p21, 6p25, 11q13, and 8q24) on 322 tumors (152 melanomas and 170 nevi) to train a new discriminatory algorithm. This new probe set was validated against 51 melanomas and 51 nevi and had a sensitivity of 94% and specificity of 98%, while the original 4-probe set had a sensitivity of 75% and specificity of 96% in the same validation set.

More recent studies have focused on diagnostic criteria using different computational algorithms. Kerl et al,⁶² however, did not find significant differences in sensitivity between 2 commonly used algorithms, used separately or combined, when applied to 163 clinically and histologically unequivocal cases of malignant melanoma.

Prognostics from fluorescence in situ hybridization testing

Key points

- **Most studies have limited long-term clinical follow-up**
- **Copy number changes at 11q13 (CCND1) and 8q24 (MYC) are associated with poor prognosis**
- **Fluorescence in situ hybridization-positive tumors may have higher risk of metastasis, but utility for prognostication is limited by poor sensitivity and specificity**

Several studies have assessed the prognostic value of the 4-probe assay. Gaiser et al⁶³ evaluated 22 melanocytic lesions (including 12 ambiguous), in which FISH results were compared with a mean clinical follow-up of 65 months. Positive FISH results had relatively poor sensitivity (60%) and specificity (50%) for later development of metastases. On the other hand, Vergier et al⁶⁴ analyzed 43 nonequivocal melanomas and nevi, for which the FISH assay achieved 85% sensitivity and 90% specificity. The same group compared the 4-probe assay with

standard histopathologic review for 90 ambiguous melanocytic tumors (including 45 spitzoid tumors) with clinical follow-up data. By comparison with outcome, the sensitivity and specificity of histopathologic review were 95% and 52%, and the sensitivity and specificity of FISH were 43% and 80%, respectively. Combining histopathologic review and FISH analysis increased sensitivity and specificity to 90% and 73%, respectively. North et al⁶⁵ also used the 4-probe assay to evaluate 144 primary melanomas with corresponding clinical outcomes. Of the lesions that later developed systemic metastases, 93% were FISH-positive, whereas only 77% of the lesions that did not metastasize were FISH-positive. FISH-positive primary tumors had a 4-fold increased risk of metastasis.

DeMarchis et al⁶⁶ applied FISH analysis to 21 tumors (including 5 melanomas, 2 tumors of uncertain malignant potential, 10 atypical Spitz tumors, and 4 Spitz nevi) from children and adolescents for which clinical follow-up (median, 51 months) was available. Chromosomal aberrations were seen in all 5 melanomas and in 1 tumor of uncertain malignant potential, in which the patient developed subsequent lymph node and distant metastasis. All remaining tumors, including all atypical Spitz tumors and Spitz nevi, were negative for gains or losses in 6 and 11q. On the other hand, Fang et al⁴⁶ showed that for 25 melanomas with known sentinel lymph node status, no statistically significant correlation was found between FISH results of the primary tumor and subsequent sentinel lymph node positivity. Gerami et al⁶⁷ used 8 probes to study 97 melanomas (55 metastasizing and 42 nonmetastasizing) for which at least 5 years of clinical follow-up were available. Copy number changes at 11q13 and 8q24 harboring CCND1 and MYC, respectively, were highly associated with poor prognosis (metastasis).

Tetzlaff et al⁶⁸ used FISH to evaluate 34 ambiguous melanocytic tumors previously reviewed by a panel of dermatopathologists (24 "favor benign" and 10 "favor malignant" lesions). FISH was positive in 3 of 24 "favor benign" lesions and in 5 of 10 "favor malignant" lesions, yielding a sensitivity of 50% and specificity of 88%. Follow-up was available for 17 of 24 "benign" lesions (mean, 16.8 months), with no recurrence or metastases reported. Of the "malignant" lesions, 8 of 10 had follow-up data (mean, 14.6 months), with 1 reported metastasis that was negative on initial FISH assay.

Gerami et al⁶⁹ evaluated atypical Spitz tumors and conventional melanomas in children. All of the atypical Spitz tumors had ≥ 1 copy number aberrations, with the presence of homozygous

9p21 deletions and a positive sentinel lymph node each found to be correlated with tumor extension beyond the sentinel lymph node. Among the conventional melanomas, copy number aberrations were present in 16 of 18 cases and 3 patients developed distant metastasis. The presence of 8q24 gains was seen almost exclusively in 6 amelanotic small cell melanomas. This group also led a multicenter study using FISH assays to evaluate 75 atypical Spitz tumors (64 with 5 years of uneventful follow-up and 11 that resulted in advanced locoregional disease, metastasis, or death).⁷⁰ Gains in 6p25 or 11q13 and homozygous deletions in 9p21 each had a significant association with aggressive clinical behavior. Shen et al⁷¹ examined outcomes of 24 atypical Spitz tumors that were found to have isolated copy number deletions in 6q23 when studied by probes targeting 6p25, 6q23, Cep6, 11q13, 9p21, and Cep9. Although 6 of 11 patients had a positive sentinel node biopsy, none of the patients developed further metastasis.

Finally, FISH testing using probes for specific genes has been used in limited prognostic studies. Bezrookove et al⁷² determined pleckstrin homology domain-interacting protein (PHIP) copy number and its relationship to ulceration in a tissue microarray containing 238 melanomas. Elevated PHIP copy number was associated with significantly reduced distant metastasis-free survival and disease-specific survival, and shown to be an independent predictor of ulceration status. Young et al⁷³ detected copy number variations in CDK4, CCND1, and CDKN2A in a cohort of 143 primary invasive melanomas. The combination of CCND1 gain with either gain of CDK4 and/or loss of CDKN2A was associated with poorer melanoma-specific survival.

RETRIEVAL OF GENETIC INFORMATION BY TAPE-STRIPPING

Technology and initial studies

Key points

- **Epidermal genetic information retrieval uses an adhesive tape to obtain RNA from the stratum corneum, which is then used to determine gene expression levels**
- **Limited studies show favorable sensitivity and specificity for melanoma using classifiers based on a small panel of genes**
- **Epidermal genetic information retrieval is not yet commercially available**

Epidermal genetic information retrieval (EGIR) technology, developed by DermTech International, Inc (La Jolla, CA), provides a minimally invasive

method for sampling RNA from stratum corneum that can be used for gene expression analysis. EGIR is referred to as “tape-stripping” because a 2-cm adhesive film is applied to a skin lesion then removed after applying direct pressure. The film can be stored frozen for a period of time before RNA is isolated then amplified, and gene expression profiles are determined using a microarray platform. Analysis of these profiles can reveal particular genes that may be differentially expressed between melanoma and the other lesions. Classification algorithms can then be developed based on a limited panel of genes.

Wachsman et al⁷⁴ used this system to develop a gene classification algorithm for differentiating melanoma from various other skin lesions. RNA was isolated from adhesive patches obtained from 202 skin lesions (including 76 melanomas) that were preselected for biopsy. Initial gene expression analysis revealed 312 genes differentially expressed between melanomas, nevi, and normal skin. Many of the genes are known to have a role in melanocyte development and physiology, melanoma, cancer, and cell growth control. Subsequent class prediction modeling of a training data set, consisting of 37 melanomas and 37 nevi, discovered a 17-gene classifier that discriminates these skin lesions. Upon testing with an independent data set consisting of 128 lesions (including 39 melanomas), this classifier discerned *in situ* and invasive melanomas from nevi with 100% sensitivity and 88% specificity. In addition, the 17-gene algorithm was also used to evaluate 73 normal skin samples, 18 pigmented basal cell carcinomas, and 22 solar lentigines; all these additional samples were negative for melanoma, except for 1 basal cell carcinoma.

Recently, Gerami et al⁷⁵ reported on the development and performance of a 2-gene classification algorithm used in combination with the tape-stripping method to differentiate melanoma from nevi. The samples were randomly selected from a biorepository containing adhesive patches from skin lesions that were subsequently biopsied. Data from a training set of 140 skin lesions (including 69 melanomas) were analyzed, and indicated that 2 genes were sufficient to confer most of the predictive value: CMIP (downregulated in melanoma) and LINC00518 (upregulated in melanoma). When tested using another set of 64 lesions (including 42 melanomas) this 2-gene classifier resulted in a sensitivity of 98% and a specificity of 73%, with a negative predictive value of 94%. These data were used to develop a second classification algorithm based on these same 2 genes and then tested against

the original 140-lesion training set, yielding a sensitivity of 97% and specificity of 68%.

There has been some discussion in the literature regarding the potential mechanisms by which transcriptional signals from melanoma cells can be derived from the stratum corneum. Grichnik⁷⁶ suggested that pagetoid cells overlying melanomas and nevi are the source of the melanocytic-specific RNA in the stratum corneum. Diaz-Cano⁷⁷ argued that most (nonulcerated) melanomas will not have sufficient numbers of cells in the stratum corneum to produce a detectable molecular signal, and alternatively suggested that melanoma-derived RNA is channeled through keratinocytes in a process similar to melanin transfer in the form of RNA-containing exosomes or microvesicles.

The EGIR system has been used for research purposes and is currently being commercialized by DermTech International, Inc.

NEW TECHNIQUES ON THE HORIZON

Key points

- New melanoma tests developed based on gene expression patterns
- Myriad Genetics' myPath is designed to be a diagnostic test
- Castle Bioscience's DecisionDx-MELANOMA is designed to be a prognostic test
- Both are commercially available

Several new molecular tests for melanoma have been developed that are also based on gene expression patterns, but the RNA is obtained from formalin-fixed paraffin-embedded sections of material obtained from biopsy specimens of lesions rather than *in situ* lesions (like EGIR). Myriad Genetics (Salt Lake City, UT) offers myPath, which is designed to be a diagnostic test to distinguish melanomas from nevi. Expression levels are assessed for 23 genes, and a numeric score is provided that indicates how similar the lesion is to nevus or to melanoma. Preliminary results have been presented at national meetings, but at this writing have not been published in peer-reviewed literature. The myPath test may best be viewed as a tool for the dermatopathologist more than for the dermatologist. The test has been applied largely to cases where there was consensus among dermatopathologists that a lesion was nevus or melanoma, and has not been rigorously applied to ambiguous melanocytic lesions; its utility for these lesions remains to be determined.

Castle Biosciences (Friendswood, TX) offers DecisionDx-MELANOMA, which is designed as a diagnostic test to assist physicians in the

management of melanoma. Based on expression levels of a panel of genes, a lesion is classified as either "low-risk" (class 1) or "high-risk" (class 2) for metastasis. Gerami et al⁷⁸ recently reported the use of the test to predict metastasis in patients initially diagnosed with stage I or II melanoma. The 28-gene signature was developed using 268 melanomas collected from 7 independent centers and then applied to a validation set consisting of 104 cases. Of these cases, 35 had developed metastatic disease and there was median follow-up of 7.3 years for the cases that did not. The 5-year disease-free survival was 97% among the 61 cases with a "low-risk" signature and 31% for the 43 cases with a "high-risk" signature. Overall, the predictor accurately identified 120 of 134 (90%) stage I/IIA cases without documented evidence of metastasis as class 1 (low-risk) and 24 of 30 (80%) stage I/IIA cases with documented metastasis as class 2 (high-risk). If DecisionDx-MELANOMA proves to be an accurate predictor of metastasis, this test may guide decision-making regarding staging procedures and adjuvant therapy. The test is currently being offered at a cost of \$7900, but patients are not being charged anything over the amount covered by their medical insurance (personal communication, March 2015).

REGULATORY APPROVAL OF MOLECULAR TESTS

It is important to note that while medical devices (such as those discussed in part I of this continuing medical education article) require approval from the US Food and Drug Administration (FDA), the molecular assays or tests discussed above do not. Rather, the laboratories that perform these tests may get a Clinical Laboratory Improvement Amendments (CLIA) certification that is administered by the Centers for Medicare and Medicaid Services (CMS) and that regulates all clinical laboratory testing performed on humans in the United States. Laboratories receive CLIA certification for a particular test, which indicates that they can reproducibly perform the test under standardized conditions. However, this process does not approach the rigor of going through the FDA approval process. CLIA certification does not take into account the clinical implications of the test, how it may impact decision-making by physicians, or potential harms to the patient based on physicians' interpretation of the test. Having access to published peer-reviewed studies on the performance of these CLIA-certified (but not FDA-approved) tests is therefore important for clinicians considering their use.

Table II. Comparison of comparative genomic hybridization and fluorescence in situ hybridization techniques

	CGH	FISH
Substrate	DNA	DNA
Probe number	Unlimited	Limited
Cost	+++	++
Accessibility	+	+++
Insurance coverage	Variable, often not	Usually covered
Advantages	Genome-based	Easier than CGH
Disadvantages	Cost, availability	Limited by probes
Sensitivity for melanoma	80-90%	80-100%
Specificity for melanoma	80-90%	95%

CGH, Comparative genomic hybridization; FISH, fluorescence in situ hybridization.

RECOMMENDATIONS

These molecular techniques provide information that cannot be gleaned from clinical or histologic examination. The most established techniques (ie, CGH and FISH) are based on detection of aberrations in cellular DNA, while the newer technologies (ie, EGIR, myPath, and DecisionDx-MELANOMA) are based on RNA (ie, gene expression). The FISH method is simpler, rapid, more accessible, and inexpensive (and more likely to be covered by insurance) compared to CGH, but is also more prone to false-negative results because only a small fraction of the genome is examined. Although there is great promise, these newer RNA-based methods have not been studied in enough detail to make any current recommendations for their use. A comparison of the 2 established molecular approaches is presented in Table II. There is also the possibility of combining molecular and imaging technologies. For example, Nardone et al⁷⁹ reported that in a subset of early melanoma cases, combining dermoscopy and FISH may enhance the detection of early melanoma. Like all diagnostic tests, those reviewed here should be considered as adjunctive tools in reaching a diagnosis and management plan once all variables are considered—including clinical examination and additional information gleaned from other diagnostic modalities.

Molecular testing has shown the potential to affect the management of melanocytic lesions of uncertain biologic behavior, particularly if uncertainty remains after histologic examination (summarized in Table III and reviewed elsewhere^{58,80-82}). The enhanced sensitivity of detecting melanoma or identifying more aggressive subtypes would change the

Table III. Summary of potential applications of molecular techniques

Facilitate diagnosis of ambiguous lesions
Predict behavior of ambiguous lesions, atypical Spitz tumors of childhood
Predict behavior of early stage melanomas
Inform staging and management decisions for melanoma patients
Inform management of severely dysplastic nevi, congenital nevi, or Spitz nevi
Predict biologic significance of rare cells in sentinel lymph nodes

management from reexcision with narrow margins if negative to wide local excision if positive. In addition, the decision to obtain a sentinel lymph node biopsy specimen, along with the ensuing costs and potential morbidity, could also be affected based on whether a lesion was deemed more likely to be a melanoma versus another neoplasm that is unlikely to metastasize. It is important to note that if the molecular test result is equivocal, then the test is not helpful for guiding treatment because the diagnosis has not been definitively established. Given sensitivities of CGH and FISH in the range of 80% to 90% (Table II), there is some inherent risk of a false-negative test down-staging a potentially malignant lesion that could have a fatal outcome. For this reason, it is reasonable to assume that most clinicians would be less conservative in monitoring histologically equivocal lesions that tested negative. Few studies have sufficient clinical follow-up on individual patients to provide meaningful prognostic information. Long-term prospective trials using molecular techniques to guide excision and staging decisions are necessary to determine the utility of down-staging particular lesions. If viable in such use, molecular studies have the significant potential to limit cost and morbidity of additional laboratory work-up and treatment.

The availability and cost of these tests also pose additional barriers to their widespread use. While CGH is primarily performed at academic research centers (and not readily available to community-based clinicians), FISH testing is more widely available. The costs of these tests range from \$1300 to \$1800 and may not be covered by insurance (particularly CGH). Another potential barrier to their use is availability of a molecular pathologist to help interpret the results.

In conclusion, these tests have significant potential to affect clinical practice in the management of melanocytic lesions. It is possible that 1 CGH

platform or 1 set of FISH probes will not be optimal for every application, and it may be important to develop more specialized panels and probes for specific clinical applications. The most acute utility appears in helping to identify aggressive tumors and adjust management accordingly. Other substantial impacts include down-staging of lesions and prediction of tumor biologic behavior; however, such applications will require additional validation by clinical trials with extensive numbers of lesions and long-term clinical follow-up.

REFERENCES

1. Piepkorn MW, Barnhill RL, Cannon-Albright LA, et al. A multiobserver, population-based analysis of histologic dysplasia in melanocytic nevi. *J Am Acad Dermatol*. 1994;30:707-714.
2. Corona R, Mele A, Amini M, et al. Interobserver variability on the histopathologic diagnosis of cutaneous melanoma and other pigmented skin lesions. *J Clin Oncol*. 1996;14:1218-1223.
3. Farmer ER, Gonin R, Hanna MP. Discordance in the histopathologic diagnosis of melanoma and melanocytic nevi between expert pathologists. *Hum Pathol*. 1996;27:528-531.
4. Lodha S, Saggar S, Celebi JT, Silvers DN. Discordance in the histopathologic diagnosis of difficult melanocytic neoplasms in the clinical setting. *J Cutan Pathol*. 2008;35:349-352.
5. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. *Hum Pathol*. 1999;30:513-520.
6. Duffy K, Grossman D. The dysplastic nevus: from historical perspective to management in the modern era: part I. Historical, histologic, and clinical aspects. *J Am Acad Dermatol*. 2012;67:1.e1-1.e16.
7. Duffy K, Grossman D. The dysplastic nevus: from historical perspective to management in the modern era: part II. Molecular aspects and clinical management. *J Am Acad Dermatol*. 2012;67:19.e1-19.e12.
8. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol*. 2011;29:2199-2205.
9. Gimotty PA, Elder DE, Fraker DL, et al. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol*. 2007;25:1129-1134.
10. Chia SK, Bramwell VH, Tu D, et al. A 50-gene intrinsic subtype classifier for prognosis and prediction of benefit from adjuvant tamoxifen. *Clin Cancer Res*. 2012;18:4465-4472.
11. Kallioniemi A, Kallioniemi OP, Sudar D, et al. Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. *Science*. 1992;258:818-821.
12. Pinkel D, Segraves R, Sudar D, et al. High resolution analysis of DNA copy number variation using comparative genomic hybridization to microarrays. *Nat Genet*. 1998;20:207-211.
13. Balaban G, Herlyn M, Guerry DT, et al. Cytogenetics of human malignant melanoma and premalignant lesions. *Cancer Genet Cytoigenet*. 1984;11:429-439.
14. Cowan JM, Halaban R, Francke U. Cytogenetic analysis of melanocytes from premalignant nevi and melanomas. *J Natl Cancer Inst*. 1988;80:1159-1164.
15. Limon J, Dal Cin P, Sait SN, Karakousis C, Sandberg AA. Chromosome changes in metastatic human melanoma. *Cancer Genet Cytoigenet*. 1988;30:201-211.
16. Bastian BC, LeBoit PE, Hamm H, Brocker EB, Pinkel D. Chromosomal gains and losses in primary cutaneous melanomas detected by comparative genomic hybridization. *Cancer Res*. 1998;58:2170-2175.
17. DiSano K, Tschen JA, Cho-Vega JH. Intratumoral heterogeneity of chromosome 9 loss and CDKN2A (p16) protein expression in a morphologically challenging spitzoid melanoma. *Am J Dermatopathol*. 2013;35:277-280.
18. Houang M, Castillo C, La Marca S, et al. An unusual case of desmoplastic melanoma containing an osteoclast-like giant cell-rich nodule. *Am J Dermatopathol*. 2015;37:299-304.
19. Bastian BC, Kashani-Sabet M, Hamm H, et al. Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. *Cancer Res*. 2000;60:1968-1973.
20. Namiki T, Yanagawa S, Izumo T, et al. Genomic alterations in primary cutaneous melanomas detected by metaphase comparative genomic hybridization with laser capture or manual microdissection: 6p gains may predict poor outcome. *Cancer Genet Cytoigenet*. 2005;157:1-11.
21. Bastian BC, Olshen AB, LeBoit PE, Pinkel D. Classifying melanocytic tumors based on DNA copy number changes. *Am J Pathol*. 2003;163:1765-1770.
22. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med*. 2005;353:2135-2147.
23. Gast A, Scherer D, Chen B, et al. Somatic alterations in the melanoma genome: a high-resolution array-based comparative genomic hybridization study. *Genes Chromosomes Cancer*. 2010;49:733-745.
24. Lazar V, Ecsedi S, Vizkeleti L, et al. Marked genetic differences between BRAF and NRAS mutated primary melanomas as revealed by array comparative genomic hybridization. *Melanoma Res*. 2012;22:202-214.
25. Bastian BC, Wesselmann U, Pinkel D, LeBoit PE. Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. *J Invest Dermatol*. 1999;113:1065-1069.
26. Harvell JD, Kohler S, Zhu S, et al. High-resolution array-based comparative genomic hybridization for distinguishing paraffin-embedded Spitz nevi and melanomas. *Diagn Mol Pathol*. 2004;13:22-25.
27. Harris K, Florell SR, Papenfuss J, et al. Melanoma mimic: a case of multiple pagetoid Spitz nevi. *Arch Dermatol*. 2012;148:370-374.
28. Held L, Eigenthaler TK, Metzler G, et al. Proliferative activity, chromosomal aberrations, and tumor-specific mutations in the differential diagnosis between blue nevi and melanoma. *Am J Pathol*. 2013;182:640-645.
29. North JP, Yeh I, McCalmont TH, LeBoit PE. Melanoma ex blue nevus: two cases resembling large plaque-type blue nevus with subcutaneous cellular nodules. *J Cutan Pathol*. 2012;39:1094-1099.
30. Held L, Metzler G, Eigenthaler TK, et al. Recurrent nodules in a periauricular plaque-type blue nevus with fatal outcome. *J Cutan Pathol*. 2012;39:1088-1093.
31. Bastian BC, Xiong J, Frieden IJ, et al. Genetic changes in neoplasms arising in congenital melanocytic nevi: differences between nodular proliferations and melanomas. *Am J Pathol*. 2002;161:1163-1169.
32. Nguyen TL, Theos A, Kelly DR, Busam K, Andea AA. Mitotically active proliferative nodule arising in a giant congenital melanocytic nevus: a diagnostic pitfall. *Am J Dermatopathol*. 2013;35:e16-e21.

33. Magro CM, Abraham RM, Guo R, et al. Deep penetrating nevus-like borderline tumors: a unique subset of ambiguous melanocytic tumors with malignant potential and normal cytogenetics. *Eur J Dermatol.* 2014;24:594-602.
34. Su A, Low L, Li X, Zhou S, Mascarenhas L, Barnhill RL. De novo congenital melanoma: analysis of 2 cases with array comparative genomic hybridization. *Am J Dermatopathol.* 2014;36:915-919.
35. Hirsch D, Kemmerling R, Davis S, et al. Chromothripsis and focal copy number alterations determine poor outcome in malignant melanoma. *Cancer Res.* 2013;73:1454-1460.
36. Boi S, Tebaldi T, Re A, et al. Increased frequency of minimal homozygous deletions is associated with poor prognosis in primary malignant melanoma patients. *Genes Chromosomes Cancer.* 2014;53:487-496.
37. Hollman P, ed. *Current procedural terminology, CPT 2014, professional edition.* 4th ed. Chicago (IL): American Medical Association; 2013.
38. Aetna website. Clinical policy bulletin: comparative genomic hybridization (CGH). Available at: http://www.aetna.com/cpb/medical/data/700_799/0787.html. Accessed March 19, 2015.
39. Anthem website. Diagnostic genetic testing of a potentially affected individual (adult or child). Available at: http://www.anthem.com/medicalpolicies/anthem/va/policies/mp_pw_b082311.htm. Accessed March 19, 2015.
40. Gerami P, Zembowicz A. Update on fluorescence in situ hybridization in melanoma: state of the art. *Arch Pathol Lab Med.* 2011;135:830-837.
41. Gerami P, Jewell SS, Morrison LE, et al. Fluorescence in situ hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. *Am J Surg Pathol.* 2009;33:1146-1156.
42. Morey AL, Murali R, McCarthy SW, Mann GJ, Scolyer RA. Diagnosis of cutaneous melanocytic tumours by four-colour fluorescence in situ hybridisation. *Pathology.* 2009;41:383-387.
43. Gerami P, Mafee M, Lurtsbarapa T, Guitart J, Haghigiat Z, Newman M. Sensitivity of fluorescence in situ hybridization for melanoma diagnosis using RREB1, MYB, Cep6, and 11q13 probes in melanoma subtypes. *Arch Dermatol.* 2010;146:273-278.
44. Abasolo A, Vargas MT, Rios-Martin JJ, Trigo I, Arjona A, Gonzalez-Campora R. Application of fluorescence in situ hybridization as a diagnostic tool in melanocytic lesions, using paraffin wax-embedded tissues and imprint-cytology specimens. *Clin Exp Dermatol.* 2012;37:838-843.
45. Zembowicz A, Yang SE, Kafanas A, Lyle SR. Correlation between histologic assessment and fluorescence in situ hybridization using MelanoSITE in evaluation of histologically ambiguous melanocytic lesions. *Arch Pathol Lab Med.* 2012;136:1571-1579.
46. Fang Y, Dusza S, Jhanwar S, Busam KJ. Fluorescence in situ hybridization (FISH) analysis of melanocytic nevi and melanomas: sensitivity, specificity, and lack of association with sentinel node status. *Int J Surg Pathol.* 2012;20:434-440.
47. Moore MW, Gasparini R. FISH as an effective diagnostic tool for the management of challenging melanocytic lesions. *Diagn Pathol.* 2011;6:76.
48. Martin V, Banfi S, Bordoni A, Leoni-Parvez S, Mazzucchelli L. Presence of cytogenetic abnormalities in Spitz naevi: a diagnostic challenge for fluorescence in-situ hybridization analysis. *Histopathology.* 2012;60:336-346.
49. Raskin L, Ludgate M, Iyer RK, et al. Copy number variations and clinical outcome in atypical spitz tumors. *Am J Surg Pathol.* 2011;35:243-252.
50. Requena C, Rubio L, Traves V, et al. Fluorescence in situ hybridization for the differential diagnosis between Spitz naevus and spitzoid melanoma. *Histopathology.* 2012;61:899-909.
51. Newman MD, Lertsburapa T, Mirzabeigi M, et al. Fluorescence in situ hybridization as a tool for microstaging in malignant melanoma. *Mod Pathol.* 2009;22:989-995.
52. Pouryazdanparast P, Newman M, Mafee M, et al. Distinguishing epithelioid blue nevus from blue nevus-like cutaneous melanoma metastasis using fluorescence in situ hybridization. *Am J Surg Pathol.* 2009;33:1396-1400.
53. Gerami P, Wass A, Mafee M, et al. Fluorescence in situ hybridization for distinguishing nevoid melanomas from mitotically active nevi. *Am J Surg Pathol.* 2009;33:1783-1788.
54. Dalton SR, Gerami P, Kolaitis NA, et al. Use of fluorescence in situ hybridization (FISH) to distinguish intranodal nevus from metastatic melanoma. *Am J Surg Pathol.* 2010;34:231-237.
55. Zulfiqar M, Thompson AD. Current applications of molecular genetic technologies to the diagnosis and treatment of cutaneous melanocytic neoplasms. *Clin Lab Med.* 2013;33:881-890.
56. North JP, Garrido MC, Kolaitis NA, et al. Fluorescence in situ hybridization as an ancillary tool in the diagnosis of ambiguous melanocytic neoplasms: a review of 804 cases. *Am J Surg Pathol.* 2014;38:824-831.
57. Song J, Mooi WJ, Petronic-Rosic V, et al. Nevus versus melanoma: to FISH, or not to FISH. *Adv Anat Pathol.* 2011;18:229-234.
58. McCalmon TH. Fillet of FISH. *J Cutan Pathol.* 2011;38:327-328.
59. Hossain D, Qian J, Adupe J, Drewnowska K, Bostwick DG. Differentiation of melanoma and benign nevi by fluorescence in-situ hybridization. *Melanoma Res.* 2011;21:426-430.
60. Gammon B, Beilfuss B, Guitart J, Gerami P. Enhanced detection of spitzoid melanomas using fluorescence in situ hybridization with 9p21 as an adjunctive probe. *Am J Surg Pathol.* 2012;36:81-88.
61. Gerami P, Li G, Pouryazdanparast P, et al. A highly specific and discriminatory FISH assay for distinguishing between benign and malignant melanocytic neoplasms. *Am J Surg Pathol.* 2012;36:808-817.
62. Kerl K, Palmedo G, Wiesner T, et al. A proposal for improving multicolor FISH sensitivity in the diagnosis of malignant melanoma using new combined criteria. *Am J Dermatopathol.* 2012;34:580-585.
63. Gaiser T, Kutzner H, Palmedo G, et al. Classifying ambiguous melanocytic lesions with FISH and correlation with clinical long-term follow up. *Mod Pathol.* 2010;23:413-419.
64. Vergier B, Prochazkova-Carlotti M, de la Fouchardiere A, et al. Fluorescence in situ hybridization, a diagnostic aid in ambiguous melanocytic tumors: European study of 113 cases. *Mod Pathol.* 2011;24:613-623.
65. North JP, Vetto JT, Murali R, et al. Assessment of copy number status of chromosomes 6 and 11 by FISH provides independent prognostic information in primary melanoma. *Am J Surg Pathol.* 2011;35:1146-1150.
66. DeMarchis EH, Swetter SM, Jennings CD, Kim J. Fluorescence in situ hybridization analysis of atypical melanocytic proliferations and melanoma in young patients. *Pediatr Dermatol.* 2014;31:561-569.
67. Gerami P, Jewell SS, Pouryazdanparast P, et al. Copy number gains in 11q13 and 8q24 [corrected] are highly linked to prognosis in cutaneous malignant melanoma. *J Mol Diagn.* 2011;13:352-358.
68. Tetzlaff MT, Wang WL, Milless TL, et al. Ambiguous melanocytic tumors in a tertiary referral center: the contribution of fluorescence in situ hybridization (FISH)

- to conventional histopathologic and immunophenotypic analyses. *Am J Surg Pathol.* 2013;37:1783-1796.
69. Gerami P, Cooper C, Bajaj S, et al. Outcomes of atypical spitz tumors with chromosomal copy number aberrations and conventional melanomas in children. *Am J Surg Pathol.* 2013;37:1387-1394.
 70. Gerami P, Scolyer RA, Xu X, et al. Risk assessment for atypical spitzoid melanocytic neoplasms using FISH to identify chromosomal copy number aberrations. *Am J Surg Pathol.* 2013;37:676-684.
 71. Shen L, Cooper C, Bajaj S, et al. Atypical spitz tumors with 6q23 deletions: a clinical, histological, and molecular study. *Am J Dermatopathol.* 2013;35:804-812.
 72. Bezrookove V, De Semir D, Nosrati M, et al. Prognostic impact of PHIP copy number in melanoma: linkage to ulceration. *J Invest Dermatol.* 2014;134:783-790.
 73. Young RJ, Waldeck K, Martin C, et al. Loss of CDKN2A expression is a frequent event in primary invasive melanoma and correlates with sensitivity to the CDK4/6 inhibitor PD0332991 in melanoma cell lines. *Pigment Cell Melanoma Res.* 2014;27:590-600.
 74. Wachsman W, Morhenn V, Palmer T, et al. Noninvasive genomic detection of melanoma. *Br J Dermatol.* 2011;164:797-806.
 75. Gerami P, Alsobrook JP II, Palmer TJ, Robin HS. Development of a novel noninvasive adhesive patch test for the evaluation of pigmented lesions of the skin. *J Am Acad Dermatol.* 2014;71:237-244.
 76. Grichnik JM. Stratum corneum RNA levels are diagnostic for melanoma. *Br J Dermatol.* 2011;164:693-694.
 77. Diaz-Cano SJ. Paratumoral gene expression profiles: promising markers of malignancy in melanocytic lesions. *Br J Dermatol.* 2011;165:702-703.
 78. Gerami P, Cook RW, Wilkinson J, et al. Development of a prognostic genetic signature to predict the metastatic risk associated with cutaneous melanoma. *Clin Cancer Res.* 2015;21:175-183.
 79. Nardone B, Martini M, Busam K, et al. Integrating clinical/dermatoscopic findings and fluorescence *in situ* hybridization in diagnosing melanocytic neoplasms with less than definitive histopathologic features. *J Am Acad Dermatol.* 2012;66:917-922.
 80. Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. *Dermatol Ther.* 2006;19:40-49.
 81. Metzler G, Eigenthaler TK, Held L, et al. Molecular genetic classification of difficult melanocytic tumors. *J Dtsch Dermatol Ges.* 2013;11(suppl 4):11-18.
 82. Bangash HK, Romegialli A, Dadras SS. What's new in prognostication of melanoma in the dermatopathology laboratory? *Clin Dermatol.* 2013;31:317-323.

Patient safety in dermatologic surgery

Part I. Safety related to surgical procedures

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Learning objectives

After completing this learning activity participants should be able to:

- 1) Critically assess potential safety issues within their specific surgical practice
- 2) Identify knowledge, competence, or performance gaps that may lead to these issues
- 3) Delineate strategies for minimizing complications for patients undergoing dermatologic surgery

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Surgical procedures involve unique elements related to patient safety. One must be aware of potential complications and safety issues within the practice of dermatologic surgery. Developing a high level of competence in skin surgery will address some safety issues, while implementing protocols and redundancies provides systems-based correction for other safety issues. We provide an in-depth review of patient safety in dermatologic surgery. In particular, we highlight the most common safety issues and methods for reducing error. (J Am Acad Dermatol 2015;73:1-12.)

Key words: dermatologic surgery; electrosurgery; Mohs micrographic surgery; office-based surgery; patient safety; skin cancer; wrong-site surgery.

With the advent of the Patient Protection and Affordable Care Act, the Physician Quality Reporting System, and increasing regulatory oversight, tracking and improving patient safety has been brought to the forefront of health care delivery. In fact, a MEDLINE search using the subject heading “patient safety” yields more than 4000 articles, with 99% of these published after 2010.

Abbreviations used:

ADE:	adverse drug event
EMI:	electromagnetic interference
ICD:	implantable cardioverter defibrillator
JCAHO:	The Joint Commission
MMS:	Mohs micrographic surgery
WSS:	wrong site, wrong person, or wrong procedure surgery

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Table I. Dermatologic surgery–related “most serious” errors listed in decreasing frequency as reported by survey participants*

Wrong-site surgery
Technical error during procedure
Inaccurate quality/quantity of specimen
Incorrect information on sample bottle/request form
Laser procedure

*Data from Watson et al.²

The impetus for much of this discussion was the Institute of Medicine’s publication of *To Err is Human: Building a Safer Health System*.¹ This report brought forward concerning data regarding hospital deaths related to medical error and gave public notoriety to the issue.

Surgical procedures involve unique elements related to patient safety. Multiple steps are often compressed into a time-sensitive window, with added complexities caused by patient comorbidities and anatomic variations. It is imperative to consider the specific challenges to patient safety in a surgical setting and then construct checkpoints to ensure optimal outcomes.

A broad survey of attendees of dermatology meetings classified reported errors into the following categories: assessment, intervention, administrative, and communication.² The 150 respondents were asked to describe their most recent and most serious errors, with the majority of mistakes categorized as assessment, intervention, or administrative problems. Of the 10 most frequently reported serious errors, 5 directly involved dermatologic surgery (Table I), with 4 others conceivably occurring in the perioperative period (ie, an incorrect clinical diagnosis, a delayed response to a test, a prescribing error, or a problem reporting results to a physician). Focusing on improving patient safety and outcomes not only protects patients but also promotes efficient health care delivery and reduced malpractice uncertainty for physicians. Part I of this continuing medical education article will review patient safety in the dermatologic surgical setting. Part II explores safety with respect to cosmetic procedures and devices.

SAFETY IN AN OFFICE-BASED SETTING

Key points

- Surgical procedures have increasingly shifted toward the outpatient or office-based setting
- Most adverse events related to outpatient or office-based surgery occur when general anesthesia is used

- Data compiled from mandatory reporting databases and a large multicenter prospective study confirm the safety of dermatologic surgery in the office-based setting
- Electrosurgery has been shown to be safe in the office-based setting

In the 1980s, surgical procedures began shifting from hospital settings to ambulatory surgical centers. By the turn of the century, many of these procedures were commonly performed in outpatient offices. It is estimated that up to 80% of operations are now performed as outpatient procedures,³ with 15% to 20% of these occurring in an office-based setting.⁴ Reports questioning the safety of office-based surgeries led to several state medical boards investigating this practice and enacting new regulations. California became the first state to pass such regulations in 1996. In 1999, a New York State senate committee determined that many physicians performing office-based surgery were practicing outside the scope of their specialty.⁵ These investigations were largely spurred by reports of fatalities during tumescent liposuction, primarily performed using general anesthesia. Data from large studies on office-based surgery were able to quell some of the regulatory uncertainty and fear of widespread harm, noting complication rates of 0.3% to 1.5%.⁶⁻¹⁰

Reported complication rates of ambulatory or office-based surgery often relate to the use of general anesthesia. Dermatologic surgery is generally performed using local or regional anesthesia—sometimes including mild sedation—and therefore the inherent risk is minimized to an even greater degree. Some of the most useful data revealing complications during office-based procedures have been compiled from a mandatory reporting database for office procedures in Florida.¹¹⁻¹⁴ Initial prospective analysis of the first year in that database revealed that most serious complications resulted from office-based liposuction when performed under general anesthesia.¹⁴ At 7 years, 174 incidents were reported, including 31 deaths. No deaths were reported in the dermatology setting, with only 4 incidents requiring hospital transfer.¹³ By 10 years, 263 procedure-related complications and 46 deaths were reported, with the majority of deaths and nearly half of hospital transfers associated with cosmetic procedures—of which most involved general anesthesia. Also, there were no further incidents involving dermatologists, leaving the specialty accounting for 1.3% of all complications at 10 years. A review of Alabama’s mandatory reporting database over 6 years revealed similar findings.¹¹ Of note, there were no reported liposuction-related deaths or

injuries in these studies when only dilute local (tumescent) anesthesia was used. Another important finding was that board certification, facility accreditation, and hospital privileges did not seem to limit the likelihood of complications. Finally, a comparison of office-based and ambulatory surgery center–based procedures revealed lower adverse event and mortality rates with office-based surgery.¹² Regulations requiring these elements may therefore not result in increased safety as intended.

Mohs micrographic surgery (MMS) is almost universally practiced in an office-based setting, and studies specifically reviewing complications with MMS support this practice. Reported complications of MMS include hemorrhage/hematoma, wound infection, wound dehiscence, flap/graft necrosis, and nerve injury, occurring in approximately 0.7% to 2.6% of surgeries.¹⁵⁻¹⁹ The largest multicenter prospective cohort of 20,821 procedures using MMS noted a 0.72% adverse event rate, the most severe of which was reported as hospitalization for infectious complications in 4 patients.¹⁷ Notably, no deaths have been reported as a complication of MMS, despite advanced age and multiple comorbidities.²⁰ Recent evidence also reveals that infection rates are unaffected by the use of nonsterile compared to sterile gloves during MMS and reconstruction, reinforcing the safety of outpatient dermatologic surgery.²¹⁻²³

Because electrosurgery is an integral component of dermatologic surgery, it is also important to consider the safety of these methods on an outpatient basis. The primary concern with respect to electrosurgery is its potential interference with implantable electrical devices, namely cardiac pacemakers and defibrillators (ICDs). Electrocautery, electrodesiccation, electrofulguration, electrocoagulation, and electrosection have varying probabilities of interference (electrocautery being least likely and electrosection most likely). A recent review of electrosurgery emphasized its safety record within dermatologic surgery, with rare cases of electromagnetic interference (EMI) causing significant device malfunction; ICDs were more susceptible than pacemakers.²⁴ A survey of 166 dermatologic surgeons revealed 25 instances of EMI, all reported when using monopolar devices. Of note, no advanced cardiac life support was required and no hospitalizations or deaths occurred as a result of adverse events, with syncope, altered mental status, palpitations, outpatient cardiologist consultation, and temporary hemodynamic instability accounting for reported events.²⁵ A recent study of hyfrecators (both monotermal and bitermal, electrodesiccation and electrofulguration methods) found

significant interference with pacemakers within 3 cm of the device and no significant interference with ICDs.²⁶ These data support the safe use of electrosurgery in the dermatology outpatient setting. It is still prudent to consider methods such as bipolar handpieces and temporary device deactivation to mitigate risk in these patients.

The American Academy of Dermatology was at the forefront of publishing guidelines regarding office-based surgery.²⁷⁻³² These guidelines, along with available evidence, support the safe practice of dermatologic surgery in the outpatient setting. They also can assuage regulators' fears, allowing for the continued access, convenience, and cost effectiveness that office-based surgery provides.

WRONG-SITE SURGERY

Key points

- **The second most common of sentinel events reported to The Joint Commission were wrong site, wrong person, or wrong procedure surgery**
- **The universal protocol, including a time out before any procedure, can limit instances of wrong-site surgery**
- **Biopsy site identification at time of definitive surgery has been shown to be a particular challenge for dermatologic surgeons**
- **There are several ways to more clearly document biopsy site locations, including photography and triangulation with fixed landmarks**

One objective of the accreditation body known as The Joint Commission (JCAHO) is to track sentinel events, including wrong site, wrong person, or wrong procedure surgery (WSS).³³ In 2012, WSS was the second most commonly reported event, just behind unintended retention of a foreign body.³⁴ This correlates with improper performance of procedures having the second highest number of malpractice claims against dermatologists,³⁵ and WSS being the most common reason for claims against surgeons who perform MMS.³⁶ A recent survey of 150 dermatologists also revealed WSS to be the most frequent serious error encountered in their practice, with 21 instances reported.²

To address these potential errors, JCAHO instituted the universal protocol in 2004,³⁷ consisting of a preprocedure verification process, marked procedure site, and time out before beginning a procedure. Despite the observance of universal protocol procedures, a 2006 study of 25 nonspine WSSs reported to a malpractice carrier between 1985 and 2004 revealed instances of WSS that still would have

occurred.³⁸ For example, when multiple similar lesions are present, patients can misidentify the particular site to be treated during preoperative verification, with the result that the surgeon may mark and treat that lesion with confidence.

A common scenario encountered in the dermatologic setting involves the identification of biopsy sites before definitive treatment. In some cases, many months have elapsed between the time of biopsy and time of treatment. Perri et al³⁹ evaluated 51 patients and found that 31% could not identify the biopsy site at the time of follow-up, especially those returning >19 days after the biopsy specimen was obtained and those having actinic keratoses treated with cryotherapy at the time that the biopsy procedure was performed. In addition, a survey of 325 MMS surgeons showed 71% reporting that >5% of patients could not identify the biopsy site at time of surgery.⁴⁰ These data were corroborated by a prospective study of 333 biopsied skin cancers referred for MMS, which found that 9% of sites were unidentifiable by the patient on the day of surgery. The only significant factor distinguishing patients who were able to locate the site and those who were not was whether the area was visible to the patient.⁴¹ The inability to definitively locate a biopsy site may lead to WSS, and when both the patient and surgeon are unaware that the site is incorrect, the event often goes unreported. Ambiguity in biopsy site identification therefore adds to the prevalence of WSS and compromises patient safety.

There have been many proposed solutions to avoid uncertainty about biopsy location, the most prevalent being photography at time of biopsy. The advantages of photography include unambiguous documentation of suspected lesions and surrounding landmarks, relatively quick utilization (ie, point and shoot), and the ability to attach the image digitally within the electronic medical record (EMR). Photography also saves time and money at the time of surgery through rapid identification of the operative site. Because of restrictions regarding protected health information, some challenges remain with respect to transferring photographs between providers, although resources exist to securely transmit images. A degree of proficiency is also required to compose and take photographs that clearly identify the lesion. One must allow for adequate lighting and/or use a flash, include surrounding landmarks in the field of view, and ensure optimal focus on the lesion in question (Fig 1).

A study of 34 patients reviewed the utility of biopsy site photography in identifying tumors referred for MMS at a single academic center. Twelve percent of blinded dermatologists and 29%



Fig 1. A good prebiopsy photograph should include adequate lighting and/or the use of a flash, include surrounding landmarks in the field of view, and ensure optimal focus on the lesion in question.

of patients were unable to locate the biopsy site at time of surgery without a photograph.⁴² A larger study involving 271 surgical sites revealed that 16.6% of sites were misidentified by patients and 5.9% of sites were misidentified by physicians without photography, even when clinical notes and diagrams were included in the assessment.⁴³ Another application of photography involves the use of patient devices to capture images, thereby avoiding the legal and technical hurdles of transferring photographs between physicians. Cell phones, tablets, and other camera-equipped devices often provide adequate resolution for site identification,^{33,34} especially when the site is marked with a pen before the picture is taken.

Other proposed methods to enhance biopsy site identification include triangulation with fixed anatomic landmarks,^{44,45} marking with ultraviolet tattoo ink,⁴⁶ evaluation with a Wood's lamp, and the performance of gauze dermabrasion or other skin manipulation. Reporting measurements from at least 2 fixed landmarks—such as the lateral canthus, oral commissure, or helical root—produces a “picture” that might be more easily transferred and does not require a camera, allowing for easy adoption by physicians (Fig 2). Marking with tattoo ink is limited by the acquisition of necessary supplies and patient and physician preferences or concerns. Skin manipulation and attempts to enhance physical examination are much less reliable aids to biopsy site identification. In cases where a site is unclear and no supplemental documentation exists, patients may need to return to their referring physician for site identification before surgery. This last option grossly inconveniences all parties involved and places an unnecessary burden on a health care system that increasingly demands efficiency. In every case, the patient and physician should be in concordance with respect to the surgical site to be treated; giving the



Fig 2. Reporting measurements from fixed anatomic landmarks such as the medial canthus and oral commissure. This example could be reported as follows: "3-mm papule located 4.1 cm from the left medial canthus and 3 cm from the left oral commissure."

patient a mirror to confirm site identification before to surgery is recommended.⁴⁷

Alam et al⁴⁸ recently reported findings from a consensus conference of dermatology experts in which an iterative approach known as the Delphi process was used to gauge best practices for avoiding site identification error. This group reviewed the available evidence regarding site identification methods and graded consensus using answers from rounds of questionnaires. Table II lists recommendations achieving "strong" consensus among participants. One can implement processes from the time of biopsy through consultation and eventual surgery, with the specific circumstances of practice setting and patient/lesion characteristics determining the appropriate intervention.

DIAGNOSTIC/PATHOLOGY ERROR

Key points

- Reports of diagnostic error in dermatologic surgery are lacking because detecting these errors can be challenging
- Specimen identification, transport, processing, and interpretation represent common areas for potential diagnostic error in dermatologic surgery
- 75% of specimen mishandling errors occur in the preanalytic phase
- Mislabeling of specimens was reported as the most common error in a recent survey of dermatologists
- Confirmation of steps by multiple persons is a simple method to detect and reduce diagnostic error

As with other patient safety concerns, there are many challenges in detecting and correcting errors in diagnosis. It has been noted that the Institute of

Table II. "Strong" recommendations resulting from a formal consensus process*

At time of biopsy	Take a high-quality photograph with ≥1 visible anatomic landmarks
Before and during consultation	Confirm with referring physician receipt of documentation used to identify site
	Have patient point to biopsy site while looking in a mirror
	Review available documentation
	Perform a physical examination of the area
	Surgeon circles/marks biopsy site
	Have patient reconfirm site after consultation and marking
	Take a photograph of marked biopsy site for medical record
	If surgeon unsure of site after consultation, ask referring physician for clarification
Day of surgery	Identify site based on documentation
	Ask patient for verbal confirmation of site
	Ask patient to point to site
	Recircle/mark the biopsy site
	Nursing/medical assistants to confirm procedure with patient

*As reported by Alam et al.⁴⁵

Medicine's report *To Err is Human* only mentions diagnostic error twice, while medication error is referred to 70 times.⁴⁹ In addition, many physicians may feel that an error in diagnosis represents an individual knowledge gap and cannot be addressed with evidence-based or systems-oriented improvements. Although the discussion of diagnostic error is still in its infancy, an estimated 10% to 30% of medical errors are considered diagnostic, with cancer being one of the most commonly missed diagnoses and delay in treatment ensuing as a common outcome.⁵⁰ Melanoma is the second most common diagnosis found in pathology-related malpractice claims, and skin cancer or melanoma was noted in 14.2% of all claims against dermatologists in 1 study.⁵¹

Obtaining a skin biopsy specimen is a central diagnostic tool in dermatologic surgery, providing key information that guides additional workup and management. The "biopsy pathway" begins with identifying and preparing the biopsy site and ends with communication of pathology results to physicians and patients (Fig 3). It is estimated that a specimen passes through the hands of >20 individuals in many institutions. Data also indicate that nearly 75% of errors with specimen mishandling occur in the preanalytic phase (ie, at the physician's office or during processing).⁵² Errors may occur along any

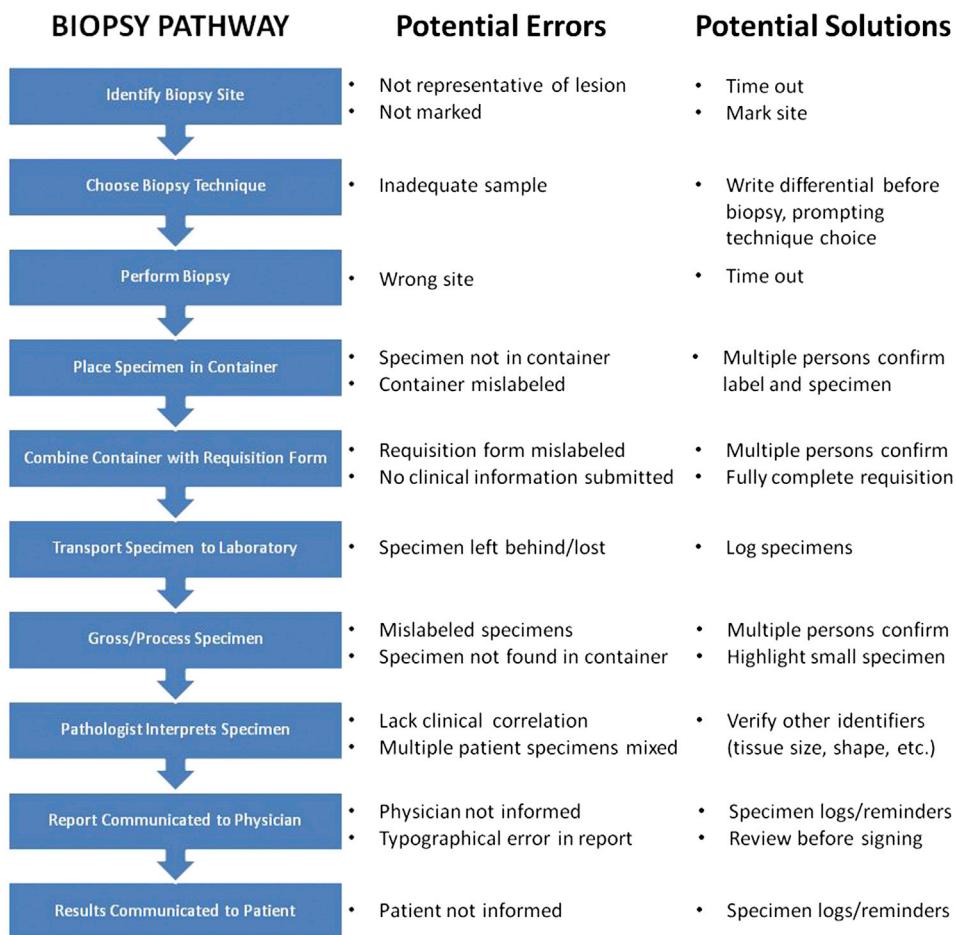


Fig 3. Biopsy pathway, including potential errors and solutions at each step of the process.

part of this pathway, resulting in incomplete or incorrect diagnoses and improper management. Because dermatologic surgery is so intricately linked with pathologic interpretation, guarding against errors can greatly improve patient safety in the specialty.

One of the first errors in the biopsy pathway that can result in patient harm is choosing the biopsy site. By definition, biopsy specimens are representative samples of a lesion and are not intended to completely remove them. One must consider the clinical differential diagnosis and then perform a biopsy that maximizes the chances of yielding a definitive pathologic diagnosis.

After obtaining a biopsy specimen, multiple errors can occur between removal, processing, and interpretation. Tissue may adhere to biopsy instruments, gauze, or even the lid of the specimen container so that a specimen may not be found when a bottle is opened in the pathology laboratory. Some submitted specimens are so small that they may be difficult to readily identify in their containers or get lost in the laboratory processing procedure.

Implementing multiple confirmations of tissue presence at various steps allows one to avoid this potential error. For example, after the physician places the specimen in the container, he/she may verbally confirm, “specimen in container,” followed by the assistant firmly closing the container, visualizing the specimen, and also confirming its presence in the container. This simple step can even be repeated for each specimen as it is passed to couriers and when received by laboratory personnel. If, at any time, an expected specimen is not identified, a time out should be called and steps to locate the tissue should be followed.

Another reported error involves the mislabeling of specimens, identified as the most common error encountered in a recent survey of dermatologists.² Labeling errors include applying specimen labels with the wrong patient information, site description, or submitting physician information. Accompanying pathology requisition forms may also be mismatched with specimens or contain inaccurate and incomplete information.

Labeling a specimen with only the patient name has been shown to increase the frequency of error.⁵³ Therefore, multiple identifiers should be used. Kim et al⁵⁴ performed a study evaluating instances of skin specimen labeling error and found 5.79 events per 1000 specimens. After instituting a safety protocol, they observed a 39% decline in this error rate. This protocol included a formalized time out procedure before the biopsy specimen was obtained and double-checking identifiers on pathology requisition forms and specimen containers, with both the physician and nursing staff initialing labels to indicate that the process was completed. One must also ensure that container lids are tightly fastened, because leaked formalin can remove ink from specimen labels. Special consideration should be given when multiple specimens are taken from a single patient, with at least 2 individuals confirming proper specimen placement and labeling throughout the process. Finally, bar codes have been shown to aid in reducing identification error, particularly when transferring patient information from labels during accessioning and pathology reporting.⁵⁵ Scanning barcodes eliminates the possibility for typographical mistakes when copying patient data, although financial barriers exist with respect to instituting barcoding technology in smaller practices and institutions.

The potential for error also exists as specimens are handed off to couriers and then to laboratory personnel. For example, specimens may be left behind or misplaced in the physician office, lost in transit, or inadvertently discarded during retrieval and processing steps. Therefore, accurate logs should be maintained documenting the number of specimens given to couriers or mailed to a laboratory, with laboratory personnel confirming receipt of the same number of specimens.

Almost half of specimen identification errors in laboratories occur during accessioning, which involves unpacking envelopes and matching forms with accompanying specimens.⁵³ Once again, confirmation by multiple persons has been shown to reduce the risk of occurrence for this type of error.⁵² Small specimens, those with significant erosions or crusting, and fragmented tissue can all hamper orientation and identification. Information should therefore be added on forms or the container to highlight small specimens and aid with orientation.

Pathologists may be more prone to make interpretive errors if the accompanying clinical information is incomplete or absent. One recent study found statistically significant differences in accurate clinicopathologic correlation when submitted clinical information was sufficient

compared to when it was incomplete or absent.⁵⁶ Also, when submitted clinical diagnoses are grossly different from histology or when histology does not match patient characteristics (eg, chronic sun damage in a child), the pathologist should pause and further investigate for potential error. Finally, routine diagnostic slide review of cases before finalizing reports has been shown to reduce the rate of amendments that change the original diagnosis or affect prognostic significance,⁵³ highlighting another useful intervention.

To complete the biopsy pathway, results must be communicated to the submitting physician and patient in a timely manner. A written report is often sent to the physician's office within days to weeks after a biopsy specimen is obtained; this report can be easily misplaced or go unread without adequate tracking. Typographical errors can also change the pathologist's intended interpretation. Finally, even after a physician has read the report and decided on a course of action, if this is not communicated to the patient then the biopsy procedure has lost its utility and the patient is potentially harmed. One survey of dermatology patients undergoing biopsies over a 3-month period found that 10% had not received their results.⁵⁷ Significant pathology (including a diagnosis of melanoma) was found in 37.8% of those who had not received their result. The investigators therefore designed an intervention that used a computerized alert system to notify the department medical manager if a pathology result was not read by a physician within 2 weeks of being issued. Follow-up patient surveys revealed a significant drop in the number of actionable results that were not communicated. Practices need to implement standardized systems and redundancies to track biopsy specimens and patient notification in order to improve safety in the biopsy pathway.

LABORATORY ERROR

Key points

- Few data exist in the dermatology literature regarding the incidence of laboratory error and resulting complications
- Failure to follow-up on laboratory results is a significant patient safety issue
- One study found that laboratory results requiring urgent action (eg, a positive culture) comprised 12.6% of results not seen or acted on by ordering physicians
- Automated electronic reminders of laboratory results may be effective at reducing delays with actionable results

Other patient safety concerns arise in the setting of presurgical laboratory testing, including blood tests when indicated. Failure to obtain tests, recognize significant values, or communicate results to patients can lead to complications and poor outcomes. Few data exist in the dermatology literature regarding the incidence of laboratory error and resulting complications. The overall rate of analytical laboratory errors has been improving over the past decade, with reported rates much lower than those of diagnostic errors in radiology.⁵⁸ This focus on improvement of laboratory processes fails to address pre- and postanalytic errors, however, leaving this significant proportion of total errors open to improvement. An international work group focused on laboratory errors was formed in 2008, identifying 34 preanalytic and 15 postanalytic quality indicators as groundwork for future studies.⁵⁸ One main aspect of ensuring preanalytic safe practices is adherence to available guidelines. A recent survey found that 20% of hospital ward staff sometimes labeled test tubes away from the patient after sampling, and 10% did not always compare patient identification with the test request. In physician offices, only 54% followed patient identification guidelines.⁵⁸

The failure to follow-up on laboratory test results remains a significant issue. An inpatient hospital study reviewed potentially actionable test results that were pending upon patient discharge, contacting the ordering physician after 72 hours (inpatient physician) or 14 days (primary care physician) after the result became available to see if the physician was aware of the result. More than half (60.6%) of results were unknown to the respondents, with 12.6% of these requiring urgent action (eg, a positive culture that necessitated antibiotics).⁵⁹ Cutaneous infections represent a significant concern in dermatologic surgery, and studies addressing the incidence of error in managing wound culture results would address a potential safety issue in the specialty. As in biopsy procedure results, a systematic method for tracking test results would certainly aid in mitigating this potential error. The same hospital system noting errors in reporting laboratory results pending at discharge devised a method for electronically notifying ordering physicians of results as they become available. A randomized controlled trial evaluated physicians using this email-based notification and those continuing without the new tool; physician awareness of results in the notification group was 3 to 6 times more likely than in the control group.⁶⁰ These data support the concept of implementing redundancies and automated systems to aid in test result notification and thereby improve patient

safety. This method can also apply to radiology test results.

MEDICATION ERROR

Key points

- Dermatologic surgeons may prescribe analgesic, anxiolytic, or antiinfective medications
- Prescribing error represents a key patient safety target with relatively straightforward improvement options
- Computerized prescribing systems do not always address prescribing errors, and additional computerized decision support systems may be needed to capture/correct errors

Medications are often used in dermatologic surgery as adjunct therapies, antiinfective prophylaxis, or postoperative pain management. Understanding safety issues that can be improved with system developments also applies to medication prescribing. Adverse drug events (ADEs) were responsible for 6.3% of malpractice claims with 1 insurer, with 73% deemed preventable and equal representation of both inpatient and outpatient settings.⁶¹ Antibiotics were among the most frequently implicated drugs, highlighting the need for dermatologic surgeons to be aware of this safety issue. Anxiolytics and opioids represent other medication classes often prescribed by dermatologic surgeons that warrant additional concern with respect to safety.

Medication errors can be divided into prescribing, dispensing, and administration errors. Most available data exist in the inpatient setting, where medication monitoring and detection of ADEs is more controlled. Friedman et al⁶² recently studied transplant patients over a 1-year period and found 149 medication errors in 93 patients, with 32% of errors leading to ADEs. Patients were determined to be the root cause of 68% of all errors, with pharmacies accounting for 10%, health care team members for 17%, and financial constraints for 5%. This study underscores certain difficulties with investigating outpatient medication error, including variables such as the total number of medications, complexity of instructions, and frequency of dosing regimens. Bedell et al⁶³ found that patient age and number of medications were the factors most strongly associated with medication misuse. One of the larger studies on outpatient medication error involved 2 health care systems with searchable EMRs. Investigators analyzed >30,000 patients over a 4-month period, applied a computer algorithm to associate medication names with terms of known adverse effects and laboratory abnormalities, then

reviewed possible instances of ADEs for confirmation and classification. They found a combined rate of 1 ADE in 7 person-years, with 11% of ADEs being deemed preventable. The search strategies most likely to detect preventable ADEs involved those looking at drug classes with symptoms and drug-laboratory associations.⁶⁴ These findings can help determine methods of addressing medication safety in practice, such as implementing measures to highlight symptom associations or suggest laboratory testing.

Prescribing error represents a key patient safety target with relatively straightforward improvement options. A study of 4 adult primary care practices screened 1879 prescriptions and found 7.6% to have at least 1 error, 1 of which was potentially life threatening.⁶⁵ Notably, comparing written prescription errors to those made using an electronic entry system yielded no statistical difference in rate, although physician reviewers determined that advanced computerized decision support could have prevented 97% of these errors. In the current environment of widespread EMRs and “meaningful use” criteria, fewer written prescriptions exist. A more recent study evaluated errors with 3850 outpatient computerized prescriptions received at a commercial pharmacy chain in 3 US states.⁶⁶ This assessment found 452 (11.7%) erroneous prescriptions, with more than one-third of these potentially leading to ADEs. Antiinfective medications represented the most common drug class incorrectly prescribed, and omitted information (eg, duration, dose, or frequency) was the most common cause for error. Therefore, electronic prescriptions do not alleviate all errors and prescribers must incorporate standardized guidelines to reduce error. Many EMR systems allow for prompts to remind prescribers when information is missing. This computerized decision support can also include common dosages of medications, a list of saved “favorites” for quick reference, and algorithms to check for cross reactions and potential allergies. Failure to carefully read the prompts or confirm the final prescription can still lead to errors. Nanji et al⁶⁶ developed specific recommendations for improving electronic entry after their multistate review of prescription errors using a wide range of computerized prescribing systems. These included: “forcing functions” that do not allow finalizing of prescriptions with incomplete drug name or dosage, unspecified “as needed” directions, and inappropriate abbreviations; automated maximum dose checking and alerts; and automatic quantity calculation based on dosage and duration entries. Any improvement in system design should include prescribers in the process to

ensure proper incorporation into clinical activities. Systems that frustrate physicians because of poor design are not likely to reduce error. The best methods would involve real-time tracking of entries and immediate feedback about potential errors rather than a notice or warnings after the physician has spent significant time filling out a prescription.

Dispensing and administration errors relate to the practice of dermatologic surgery in the setting of providing antibiotics, anxiolytics, anesthetics, and analgesics on the day of surgery. Whereas nearly half of prescribing errors are detected before dispensing drugs, only 2% of administration errors are detected and corrected.⁶⁷ Factors that may lead to mistakes while administering medications include the following: the lack of standardized concentrations/formulations of medications, incomplete patient documentation regarding current medications and allergies, the absence of labels, similar appearing containers for medications, and the interruption of personnel in the process of preparing and administering a medication. For example, one scenario that may be encountered during dermatologic procedures is a reported allergy to local anesthetic. Contact allergy to topical preparations of ester anesthetics is more common, while true immunoglobulin E-mediated hypersensitivity to amide class local anesthetics is <1%.⁶⁸ Clinicians must identify these patients, review the pertinent history, and arrange for appropriate testing/challenge before administration. The literature lacks applicable studies related to the incidence of medication administration error in outpatient dermatology practice. Evidence seems to suggest that interruptions are a key contributor to such errors in the hospital setting. A recent systematic review of studies involving medication administration error and possible interventions found a paucity of evidence to support any given intervention.⁶⁹ Until data exist to support specific preventative measures, individual practices may apply principles of prudence to identify and address administration errors. These may include having 2 staff members confirm all medication dosages before administration, repeating and confirming verbal requests for medicines before administration, double-checking allergy information with patients before giving them a medication, clearly labeling medications in the office with conspicuous color coding, standardized containers, or a barcoding system, and posting quiet zone signage in medication preparation areas.⁶⁹

CONCLUSION

The culture of health care at large is developing an increased focus on quality improvement and patient

Table III. Suggested items to include in a perioperative checklist during dermatologic surgery

Allergies reviewed (eg, medications/latex/adhesives)
Preoperative antibiotics given (if indicated)
Operative site correctly identified and marked
Pathology report reviewed (if applicable)
Precautions taken for pacemaker/defibrillator
Patient anticoagulation status
Informed consent obtained
Check vital signs
Time out performed (correct patient/site)
Postoperative antibiotic/pain prescription given (if indicated)
Specimens correctly labeled and in container

safety. Surgical procedures in dermatology are particularly susceptible to scrutiny because they involve defined processes and multiple measurable outcomes. Errors in dermatologic surgery can also have visible and lasting consequences. Some errors result from a simple lack of knowledge by medical providers and can only be corrected with continuous study of the relevant medical literature. This review attempts to highlight systems errors in dermatologic surgery that are more amenable to correction by implementing standardized processes, checklists (Table III), redundancies, or other systems-based improvements.

The evidence clearly supports the safety of dermatologic surgery in the outpatient setting. One of the most significant errors continues to involve WSS, and implementing processes that confirm accurate site and patient identification will greatly aid in preventing these mistakes. Using redundancies, logs, and checklists at steps along the biopsy pathway may reduce error throughout this multistep process. Similar strategies may also aid in preventing errors with communicating laboratory results and prescribing or administering medications. A culture of patient safety is the key to successful endeavors in this vital aspect of quality improvement.

REFERENCES

- Kohn LT, Corrigan J, Donaldson MS. *To err is human: building a safer health system*. Washington (DC): National Academy Press; 2000.
- Watson AJ, Redbord K, Taylor JS, Shippy A, Kostecki J, Sverlick R. Medical error in dermatology practice: development of a classification system to drive priority setting in patient safety efforts. *J Am Acad Dermatol*. 2013;68:729-737.
- Horton JB, Janis JE, Rohrich RJ. MOC-PS(SM) CME article: patient safety in the office-based setting. *Plast Reconstr Surg*. 2008;122:1-21.
- del Junco R, Alpert B, Anderson LS, et al. *Report of the Special Committee on Outpatient (Office-Based) Surgery*. Washington (DC): Federation of State Medical Boards; 2002.
- Quattrone MS. Is the physician office the wild, wild west of health care? *J Ambul Care Manage*. 2000;23:64-73.
- Morello DC, Colon GA, Fredricks S, Iverson RE, Singer R. Patient safety in accredited office surgical facilities. *Plast Reconstr Surg*. 1997;99:1496-1500.
- Hoefflin SM, Bornstein JB, Gordon M. General anesthesia in an office-based plastic surgical facility: a report on more than 23,000 consecutive office-based procedures under general anesthesia with no significant anesthetic complications. *Plast Reconstr Surg*. 2001;107:243-251.
- Bitar G, Mullis W, Jacobs W, et al. Safety and efficacy of office-based surgery with monitored anesthesia care/sedation in 4778 consecutive plastic surgery procedures. *Plast Reconstr Surg*. 2003;111:150-156.
- Byrd HS, Barton FE, Orenstein HH, et al. Safety and efficacy in an accredited outpatient plastic surgery facility: a review of 5316 consecutive cases. *Plast Reconstr Surg*. 2003;112:636-641.
- Keyes GR, Singer R, Iverson RE, et al. Analysis of outpatient surgery center safety using an internet-based quality improvement and peer review program. *Plast Reconstr Surg*. 2004;113:1760-1770.
- Starling J 3rd, Thosani MK, Coldiron BM. Determining the safety of office-based surgery: what 10 years of Florida data and 6 years of Alabama data reveal. *Dermatol Surg*. 2012;38:171-177.
- Venkat AP, Coldiron B, Balkrishnan R, et al. Lower adverse event and mortality rates in physician offices compared with ambulatory surgery centers: a reappraisal of Florida adverse event data. *Dermatol Surg*. 2004;30:1444-1451.
- Coldiron BM, Healy C, Bene NI. Office surgery incidents: what seven years of Florida data show us. *Dermatol Surg*. 2008;34:285-291.
- Coldiron B. Patient injuries from surgical procedures performed in medical offices. *JAMA*. 2001;285:2582.
- Otley CC, Fewkes JL, Frank W, Olbricht SM. Complications of cutaneous surgery in patients who are taking warfarin, aspirin, or nonsteroidal anti-inflammatory drugs. *Arch Dermatol*. 1996;132:161-166.
- Cook JL, Perone JB. A prospective evaluation of the incidence of complications associated with Mohs micrographic surgery. *Arch Dermatol*. 2003;139:143-152.
- Alam M, Ibrahim O, Nodzenski M, et al. Adverse events associated with mohs micrographic surgery: multicenter prospective cohort study of 20 821 cases at 23 centers. *JAMA Dermatol*. 2013;149:1378-1385.
- Merritt BG, Lee NY, Brodland DG, Zitelli JA, Cook J. The safety of Mohs surgery: a prospective multicenter cohort study. *J Am Acad Dermatol*. 2012;67:1302-1309.
- Elliott TG, Thom GA, Litterick KA. Office based dermatological surgery and Mohs surgery: a prospective audit of surgical procedures and complications in a procedural dermatology practice. *Australas J Dermatol*. 2012;53:264-271.
- Delaney A, Shimizu I, Goldberg LH, MacFarlane DF. Life expectancy after Mohs micrographic surgery in patients aged 90 years and older. *J Am Acad Dermatol*. 2013;68:296-300.
- Xia Y, Cho S, Greenway HT, Zelac DE, Kelley B. Infection rates of wound repairs during Mohs micrographic surgery using sterile versus nonsterile gloves: a prospective randomized pilot study. *Dermatol Surg*. 2011;37:651-656.
- Mehta D, Chambers N, Adams B, Gloster H. Comparison of the prevalence of surgical site infection with use of sterile versus nonsterile gloves for resection and reconstruction during Mohs surgery. *Dermatol Surg*. 2014;40:234-239.
- Rogers HD, Desciak EB, Marcus RP, Wang S, MacKay-Wiggan J, Eliezzi YD. Prospective study of wound infections in Mohs micrographic surgery using clean surgical technique in the

- absence of prophylactic antibiotics. *J Am Acad Dermatol.* 2010;63:842-851.
24. Howe N, Cherpelis B. Obtaining rapid and effective hemostasis: part II. Electrosurgery in patients with implantable cardiac devices. *J Am Acad Dermatol.* 2013;69:677.e1-e9.
 25. El-Gamal HM, Dufresne RG, Saddler K. Electrosurgery, pacemakers and ICDs: a survey of precautions and complications experienced by cutaneous surgeons. *Dermatol Surg.* 2001;27:385-390.
 26. Weyer C, Siegle RJ, Eng GG. Investigation of hyfrecators and their in vitro interference with implantable cardiac devices. *Dermatol Surg.* 2012;38:1843-1848.
 27. Guidelines of care for office surgical facilities. Part I. *J Am Acad Dermatol.* 1992;26(5 pt 1):763-765.
 28. Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for office surgical facilities. Part II. Self-assessment checklist. American Academy of Dermatology. *J Am Acad Dermatol.* 1995;33:265-270.
 29. Drake LA, Dinehart SM, Goltz RW, et al. Guidelines of care for Mohs micrographic surgery. American Academy of Dermatology. *J Am Acad Dermatol.* 1995;33:271-278.
 30. Guidelines of care for dermabrasion. American Academy of Dermatology Committee on Guidelines of Care. *J Am Acad Dermatol.* 1994;31:654-657.
 31. Guidelines of care for cryosurgery. American Academy of Dermatology Committee on Guidelines of Care. *J Am Acad Dermatol.* 1994;31:648-653.
 32. Dover JS, Arndt KA, Dinehart SM, Fitzpatrick RE, Gonzalez E. Guidelines of care for laser surgery. American Academy of Dermatology. Guidelines/Outcomes Committee. *J Am Acad Dermatol.* 1999;41:484-495.
 33. A follow-up review of wrong site surgery. *Sentinel Event Alert.* 2001;1-3.
 34. Sentinel event statistics for 2012. *Jt Comm Perspect.* 2013;33, 1, 3.
 35. Elston DM, Taylor JS, Coldiron B, et al. Patient safety: part I. Patient safety and the dermatologist. *J Am Acad Dermatol.* 2009;61:179-190.
 36. Perlis CS, Campbell RM, Perlis RH, Malik M, Dufresne RG Jr. Incidence of and risk factors for medical malpractice lawsuits among Mohs surgeons. *Dermatol Surg.* 2006;32:79-83.
 37. JCAHO's universal protocol released to widespread endorsement. *Jt Comm Perspect.* 2004;24:1-4.
 38. Kawa MR, Studdert DM, Zinner MJ, Gawande AA. Incidence, patterns, and prevention of wrong-site surgery. *Arch Surg.* 2006;141:353-357.
 39. Perri AJ 3rd, Chan C, Uchida T, Wagner R Jr. Patients' recall of visible skin biopsy sites. *Skin Cancer.* 2008;23:61-67.
 40. Nemeth SA, Lawrence N. Site identification challenges in dermatologic surgery: a physician survey. *J Am Acad Dermatol.* 2012;67:262-268.
 41. Rossy KM, Lawrence N. Difficulty with surgical site identification: what role does it play in dermatology? *J Am Acad Dermatol.* 2012;67:257-261.
 42. Ke M, Moul D, Camouse M, et al. Where is it? The utility of biopsy-site photography. *Dermatol Surg.* 2010;36:198-202.
 43. McGinness JL, Goldstein G. The value of preoperative biopsy-site photography for identifying cutaneous lesions. *Dermatol Surg.* 2010;36:194-197.
 44. Pagliarello C, Paradisi A, Dianzani C, Paradisi M, Persichetti P. Avoiding surgical errors by referencing anatomical landmarks. *Br J Dermatol.* 2012;167:951-952.
 45. MacFarlane DF, Wysong A. A schema using fixed anatomic landmarks for biopsy site identification on the head and neck. *Dermatol Surg.* 2013;39:1705-1708.
 46. Chuang GS, Gilchrest BA. Ultraviolet-fluorescent tattoo location of cutaneous biopsy site. *Dermatol Surg.* 2012;38:479-483.
 47. Al-Rawi H, Varma S. The use of a hand-held mirror to reduce litigation and improve communication in dermatological surgery. *Br J Dermatol.* 2012;167:446-447.
 48. Alam M, Lee A, Ibrahim OA, et al. A multistep approach to improving biopsy site identification in dermatology: physician, staff, and patient roles based on a Delphi consensus. *JAMA Dermatol.* 2014;150:550-558.
 49. Newman-Toker DE, Pronovost PJ. Diagnostic errors—the next frontier for patient safety. *JAMA.* 2009;301:1060-1062.
 50. Schiff GD, Kim S, Abrams R, et al. Diagnosing diagnosis errors: lessons from a multi-institutional collaborative project. In: Henriksen K, Battles JB, Marks ES, Lewin DL, eds. *Advances in patient safety: from research to implementation; Vol 2. Concepts and methodology.* Rockville (MD): Agency for Healthcare Research and Quality; 2005.
 51. Marsch A, High WA. Medicolegal issues with regard to melanoma and pigmented lesions in dermatopathology. *Dermatol Clin.* 2012;30:593-615.
 52. Weyers W. Confusion-specimen mix-up in dermatopathology and measures to prevent and detect it. *Dermatol Pract Concept.* 2014;4:27-42.
 53. Nakhlé RE, Zarbo RJ. Surgical pathology specimen identification and accessioning: a College of American Pathologists Q-Probes Study of 1 004 115 cases from 417 institutions. *Arch Pathol Lab Med.* 1996;120:227-233.
 54. Kim JK, Dotson B, Thomas S, Nelson KC. Standardized patient identification and specimen labeling: a retrospective analysis on improving patient safety. *J Am Acad Dermatol.* 2013;68:53-56.
 55. Howanitz PJ. Errors in laboratory medicine: practical lessons to improve patient safety. *Arch Pathol Lab Med.* 2005;129:1252-1261.
 56. Aslan C, Goktay F, Mansur AT, Aydingoz IE, Gunes P, Ekmekekci TR. Clinicopathological consistency in skin disorders: a retrospective study of 3949 pathological reports. *J Am Acad Dermatol.* 2012;66:393-400.
 57. Topol P, Porat N, Zelker R, Ingber A, Zlotogorski A, Brezis M. Quality improvement program to assure the delivery of pathology test results: a systemic intervention in a large general hospital. *Dermatol Nurs.* 2007;19:253-257.
 58. Lippi G, Becan-McBride K, Behulova D, et al. Preanalytical quality improvement: in quality we trust. *Clin Chem Lab Med.* 2013;51:229-241.
 59. Roy CL, Poon EG, Karson AS, et al. Patient safety concerns arising from test results that return after hospital discharge. *Ann Intern Med.* 2005;143:121-128.
 60. Dalal AK, Roy CL, Poon EG, et al. Impact of an automated email notification system for results of tests pending at discharge: a cluster-randomized controlled trial. *J Am Med Inform Assoc.* 2014;21:473-480.
 61. Rothschild JM, Federico FA, Gandhi TK, Kaushal R, Williams DH, Bates DW. Analysis of medication-related malpractice claims: causes, preventability, and costs. *Arch Intern Med.* 2002;162:2414-2420.
 62. Friedman AL, Geoghegan SR, Sowers NM, Kulkarni S, Formica RN Jr. Medication errors in the outpatient setting: classification and root cause analysis. *Arch Surg.* 2007;142:278-283.
 63. Bedell SE, Jabbour S, Goldberg R, et al. Discrepancies in the use of medications: their extent and predictors in an outpatient practice. *Arch Intern Med.* 2000;160:2129-2134.

64. Gandhi TK, Seger AC, Overhage JM, et al. Outpatient adverse drug events identified by screening electronic health records. *J Patient Saf.* 2010;6:91-96.
65. Gandhi TK, Weingart SN, Seger AC, et al. Outpatient prescribing errors and the impact of computerized prescribing. *J Gen Intern Med.* 2005;20:837-841.
66. Nanji KC, Rothschild JM, Salzberg C, et al. Errors associated with outpatient computerized prescribing systems. *J Am Med Inform Assoc.* 2011;18:767-773.
67. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA.* 1995;274:35-43.
68. Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth.* 2012;108:903-911.
69. Raban MZ, Westbrook JI. Are interventions to reduce interruptions and errors during medication administration effective?: a systematic review. *BMJ Qual Saf.* 2014;23:414-421.

Patient safety in procedural dermatology

Part II. Safety related to cosmetic procedures

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Learning objectives

After completing this learning activity, participants should be able to:

- 1) Critically assess potential safety issues within their specific cosmetic practice
- 2) Identify knowledge, competence, or performance gaps that may lead to these issues
- 3) Delineate strategies for minimizing complications for patients undergoing cosmetic procedures

Disclosures

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Cosmetic procedures are growing in popularity and are associated with unique risks. Considering potential complications and prioritizing patient safety will help practitioners improve outcomes of elective procedures. In part II of this continuing medical education article, we provide a comprehensive review of patient safety in cosmetic procedures, including medical and legal issues surrounding the supervision and training of physician extenders. (J Am Acad Dermatol 2015;73:15-24.)

Key words: botulinum toxins; lasers, light, and radiofrequency devices; patient safety; physician extenders; soft tissue fillers.

Advancements in dermatologic surgery over the past decade have led to an exponential increase in the number of cosmetic procedures. Between 2001 and 2007, the number of cosmetic and noncosmetic surgical procedures performed increased from 3.4 to 7.6 million—a 120.2% increase. Soft tissue augmentation and neurotoxin injections have grown most rapidly (405% and 324.4%, respectively). Not far behind, nonablative skin rejuvenation—which includes laser, light, and radiofrequency sources—saw a 330.7% growth rate,

while ablative resurfacing procedures increased by 66.8%.^{1,2} According to the American Society for Aesthetic Plastic Surgery's cosmetic surgery statistics, the top 3 nonsurgical procedures in the United States in 2013 were neurotoxin injection, soft tissue augmentation, and hair removal.³

Our understanding of the safety profile of various cosmetic procedures has also grown over the years, and techniques have therefore improved significantly. Awareness of the potential complications of cosmetic procedures and a focus on patient safety

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has helped improve the outcomes and efficacy of these procedures and helped protect physicians from potential liability. Part II of this continuing medical education article will review the safety of various cosmetic procedures and explore potential issues and complications caused by physician extenders.

NEUROTOXIN SAFETY

Key points

- **Botulinum toxin products were first developed in 1989 and were approved by the US Food and Drug Administration in 2002 for the treatment of glabellar lines**
- **The 3 botulinum toxin type A products used in the United States are onabotulinumtoxin A, abobotulinumtoxin A, and incobotulinumtoxin A**
- **Common side effects include injection site reactions, headaches, muscle weakness, and ptosis**
- **Non-injection site complications result from the improper placement of toxin or from local diffusion into unintended adjacent muscles**
- **Injection technique, injection volumes, concentration gradients, and anatomic boundaries influence local diffusion**

Botulinum neurotoxin products are the most popular nonsurgical cosmetic procedure. In 1989, the first neurotoxin onabotulinumtoxin A (BOTOX Cosmetic; Allergan Inc, Irvine, CA), was developed for the treatment of blepharospasm and strabismus, and was subsequently approved for the treatment of glabellar lines until 2002.⁴ Since then, its clinical uses (both on- and off-label) have broadened, and many products have been developed. In the United States, botulinum toxin type A derivatives used for facial lines also include abobotulinumtoxin A (Dysport; Medicis Aesthetics, Scottsdale, AZ) and incobotulinumtoxin A (Xeomin; Merz Aesthetics, Frankfurt, Germany). Overall, these products are associated with favorable side effect profiles.

Common reported side effects include injection site reactions (ie, erythema, pain, pruritus, rash, and ecchymosis), short-term hyperesthesia, muscle weakness, ptosis, headache, and lack of intended cosmetic effect.⁴ A minority of patients (approximately 1%) may experience idiosyncratic severe headaches.⁵ Non-injection site complications typically result from the improper placement of toxin or from local diffusion into unintended adjacent muscles. Injection technique, injection volumes, concentration gradients, and anatomic boundaries influence

local diffusion. Lid ptosis is a well-known complication of glabellar injection. Various studies have been conducted to evaluate the frequency of its occurrence, which has ranged from 2% to 20%. A multicenter, double-blind, randomized clinical trial of the safety and tolerability of onabotulinumtoxin A reported ptosis at a rate of approximately 5%.⁶ However, injection techniques have advanced, and recent studies have reported rates as low as 1%. Another less common complication is drooping of the lips caused by weakening of the zygomaticus major muscle during crow's feet injection. In a study of 1000 patients, only 3 patients developed this complication. In all 3 cases, 15 units (or 7.5 U/side) were used.⁷

Onabotulinumtoxin A

Onabotulinumtoxin A injection is the most performed cosmetic procedure, and therefore its safety and tolerability have been widely studied. Complication rates differ between injection sites and with different doses. Generally, a higher risk of complications is associated with glabellar compared to lateral canthal injections. A metaanalysis of the safety of onabotulinumtoxin A for facial lines was published in the *Journal* in 2009⁸ and included studies evaluating the treatment of both the glabella and lateral canthus (crow's feet). The selected studies included 6 randomized, double blind, placebo-controlled and 3 open-label studies. Overall treatment-related adverse effects (TRAEs) were significantly more common in the onabotulinumtoxin A treatment group than the placebo group. Eyelid sensory abnormalities, edema, and lid ptosis reached statistical significance for the glabella but not for crow's feet. There was no evidence of muscle weakness distant from the injection site or central nervous system effects. The most common adverse event was headache (9% glabella; 4% crow's feet), but there was no significant difference in headache incidence between placebo and onabotulinumtoxin A injection (Table I). The authors interpreted the occurrence of headache as being related to the physical injection rather than the pharmacologic effect of the drug. Interestingly, the incidence of reported adverse events significantly decreased with subsequent treatments. All TRAEs were mild to moderate in severity; no serious TRAEs were documented.

Abobotulinumtoxin A

Abobotulinumtoxin A is a more recent formulation of botulinum toxin that is used to treat glabellar lines and crow's feet. It is important to note that abobotulinum A is dosed approximately 3-fold

Table I. Onabotulinumtoxin A complications*

Complication type	Percent affected after glabellar injection		Percent affected after periocular injection	
	20 U Toxin	Placebo	6-36 U Toxin	Placebo
Overall adverse events	23.6 ^t	16.1	21.1	16.7
Headache	9.0	8.5	4.8	1.7
Eyelid sensory disruption	2.6 ^t	0.4	0.0	0.0
Eyelid ptosis	2.4 ^t	0.0	0.0	0.0
Injection site pain	1.5	1.3	0.5	1.7
Eyelid edema	1.3 ^t	0.0	0.5	0.0
Injection site bruising	0.3	0.4	3.3	6.7
Injection site hematoma	0.0	0.0	4.3	1.7
Facial pain	1.1	0.0	0.5	0.0

*Data modified from Brin et al.⁸^tP < .05.

higher than the other 2 toxins discussed here. In a multicenter, phase II, randomized study comparing the efficacy of abobotulinum A toxin 50 U to placebo, 67% of patients experienced TRAEs, 4% of which were considered severe. The most frequently reported TRAEs were headaches, migraines, and eye disorders. The overall incidence of eyelid ptosis was 3.2%.⁹ In another phase III, randomized, placebo-controlled clinical trial on 544 patients receiving a single treatment of either 50, 60, 70, or 80 U, only 13 patients (2%) developed ptosis, which was mild in severity. The incidence of adverse events was not dose-related. This study also found that patients previously treated with abobotulinumtoxin A had a lower incidence of ocular and injection site TRAEs than patients who had not undergone any previous treatment.¹⁰ In a study by Kane et al,¹⁰ 3% of patients (n = 105) treated with abobotulinumtoxin A 50 U developed eyelid ptosis and blepharospasm, in comparison to another 50-U, phase III, multicenter study that found a similar rate of 4% ptosis and 1% blepharospasm. The incidence of headaches in various clinical trials has ranged from 3% to 15%.⁹

Incobotulinumtoxin A

Incobotulinumtoxin A is a novel neurotoxin that differs from the others discussed here in that it does not contain complexing proteins. This low protein content is theorized to produce fewer neutralizing antibodies and reduce treatment failure. Data supporting this claim are scarce. One randomized, double-blind, split-face trial compared head to head the safety and efficacy of onabotulinumtoxin A and incobotulinumtoxin A for periocular rhytids and masseter hypertrophy. These authors found no significant difference in efficacy or safety profile

between the 2 toxins.¹¹ In 3 placebo-controlled trials in which 535 subjects with glabellar lines received incobotulinumtoxin A 20 U, the most frequent adverse events were headache (5.4%), brow ptosis (0.7%), inject site hematoma (0.6%), and eyelid edema (0.4%).¹² In an open-label, multiple-dose trial,¹³ 13.1% of subjects reported adverse events, with headache being the most common (7.1%), followed by injection side hematoma (1%). Brow ptosis, eyelid edema, elevation of the eyebrow was reported in <1% of patients.¹³ Neutralizing antibodies against incobotulinumtoxin A were not found in any patients.

CONSEQUENCES AND LITIGATION

Key point

- The use of neurotoxins in dermatology is safe and is associated with a low incidence of adverse events and lawsuits

As shown in the aforementioned studies, the use of neurotoxins in dermatology is generally safe. Between 1989 and 2003, 36 serious adverse events and 0 deaths were reported to the US Food and Drug Administration (FDA) with the cosmetic use of onabotulinumtoxin A. More than one-third of these complications were related to off-label treatments. In contrast, during the same period, 217 serious adverse events were reported because of the therapeutic use of onabotulinumtoxin A. This is largely because of a 4-fold higher median dose (100 U vs 25 U) in therapeutic cases.¹⁴ Lawsuits related to botulinum toxins are uncommon. A study of litigation between 1985 and 2012 found 24 relevant cases, all involving onabotulinumtoxin A. Lawsuits were 5 times more likely in therapeutic use of toxins with cases citing up to 600 U dosed. Allergan, Inc was named in all cases; in only 3 cases were physicians named as codefendants. Only 1 case involved a dermatologist.⁴

SOFT TISSUE FILLER SAFETY

Key points

- The most common soft tissue fillers approved by the US Food and Drug administration are hyaluronic acid, calcium hydroxyapatite, and poly-L-lactic acid
- Adverse events include small nodule formation, foreign body granulomas, noninflammatory nodules, hypersensitivity reactions, and vascular-mediated events

Soft tissue fillers have gained popularity over the past decade largely because of their desirable results and low side effect profiles, in comparison to their predecessors, silicone and bovine collagen, which

Table II. Soft tissue filler adverse events

Adverse event	Filler associated with event	Incidence
Injection site reactions (ie, erythema, swelling, pain, and bruising)	HA, PLLA, and CaHA	Common
Foreign body granuloma	HA	Rare
Nodule formation	PLLA > CaHA	Rare
Vascular compromise	HA, PLLA, and CaHA	Rare
Hypersensitivity reactions	HA, PLLA, and CaHA	Rare
Cellulitis	CaHA	Rare

CaHA, Calcium hydroxyapatite; HA, hyaluronic acid; PLLA, poly-L-lactic acid.

are associated with a high rate of delayed onset foreign body granulomas. There was a 324% increase in the number of soft tissue augmentation treatments between 2001 and 2007. Because of their popularity, an increasing number and variety of dermal fillers are being developed to treat wrinkles, scars, and lipodystrophy. Overall, filling agents are considered to be very safe, and each product has unique associated benefits and risks. The most commonly reported adverse events include transient reactions, namely swelling and bruising. Our understanding of these reactions can help improve patient outcome and satisfaction.

The FDA-approved fillers commonly used for soft tissue augmentation included in this discussion are hyaluronic acid (HA) fillers, calcium hydroxylapatite (CaHA), and poly-L-lactic acid (PLLA). Complications may be categorized into injection site reactions, adverse effects from improper technique, allergy and hypersensitivity reactions, and vascular-mediated events (Table II). Injection site reactions include edema, pain, erythema, pruritus, and infection. Adverse effects from improper technique include small nodule formation, which is most commonly seen with superficial injection of HA fillers causing a Tyndall effect.

Foreign body granulomas are inflammatory lesions that develop months to years after injection. They are rare and their incidence ranges based on the substance used. In a cohort study of >450 patients, HA fillers were associated with the highest rate of granuloma formation (~0.4%) in comparison to CaHA (0.001%).¹⁵ CaHA has the lowest rate of granuloma formation of all dermal fillers.¹⁶ In a multicenter clinical trial of 113 patients injected with CaHA, only 7 minor adverse reactions were reported, none of which were foreign body granulomas.¹⁷

Hypersensitivity or allergic reactions can occur depending on the type of filler used.¹⁸ Hypersensitivity reactions, such as facial angioedema, have been rarely reported, and an incidence of

0.5% has been proposed in the literature.¹⁹ Nodule formation sometimes occurs as product accumulates without generating an immune response, as in a granuloma. Nodule formation is typically delayed from the time of injection and is associated more commonly with PLLA and CaHA.¹⁸ Nodules may occur because of poor placement in highly mobile areas, such as the lips, or because of poor mixing of the product.²⁰ A 5% to 8% rate of nodule formation has been reported in the literature when CaHA is injected in the lips.¹⁷

Nodules are most commonly seen with use of PLLA. The prevalence of nodule formation varies widely in clinical studies, from 6% to 52%. Two separate European studies have studied the occurrence of these nodules in patients treated with PLLA for HIV-related lipoatrophy. Nodule formation was documented in 52% and 31% of patients in each of these studies, respectively, and the average time of onset was 7 months.^{21,22} In 2 separate US studies, a lower incidence was noted, but patients were only followed for 1 year, in comparison to the European studies where patients had 2 years of follow-up. In these 2 studies, nodules occurred in 6% and 13% of patients.^{23,24} In a more recent study from 2011, 116 patients were treated with PLLA and followed for 13 months. Ten of 116 patients (8.6%) developed nodules <5 mm in diameter, and 8 of 116 patients (6.9%) developed nodules >5 mm in diameter. The mean duration of these nodules is unknown.²⁵⁻²⁸ One retrospective study reported spontaneous resolution in 23% (6/26) of patients over 2 years.²⁴

Studies have shown that both proper preparation and injection technique can minimize the formation of nodules without compromising a given filler's efficacy.²⁴ Studies have shown that nodule formation is associated with a higher concentrated suspension of PLLA. Reconstituting with 3 to 4 mL of sterile water for injection was associated with a >30% rate of nodule formation in 2 large HIV studies.^{29,30} Another study noted that the use of a dilute suspension (approximately 5 mL) is associated with a reduction in nodule formation to <5%.³¹⁻³³ Granulomas can be difficult to differentiate from fibrotic nodules, but characteristics more common of nodules include later onset, tenderness, swelling, and erythema. Nodule formation after treatment with HA has been reported but is much less common than the aforementioned products.

Vascular-mediated events are perhaps the most dreaded complication of soft tissue augmentation, and they may result in skin necrosis. The glabella is a high-risk anatomic location for ischemic necrosis. Blood supply to the glabella is poor, being largely provided by small branches from the supratrochlear



Fig 1. Filler necrosis.

and supraorbital arteries. Necrosis can occur via vessel injury, compression, or occlusion of these branches and their tributaries.³⁴ Retinal embolism with intravascular injection of the supratrochlear artery has also been described.²¹ Though less common, alar necrosis has also been reported after injection of the nasolabial fold. This likely occurs because of compression of the angular artery or branches in this region.²² In a retrospective review of 2089 soft tissue filler injections, 1 patient (<0.05%) experienced intravascular compromise and subsequent alar necrosis after CaHA injections.²³ Given the morbidity of these complications, it is recommended that injectors withdraw the plunger of the syringe to examine for a flash of blood to mitigate the risk of intravascular injection. In the German Injectable Filler Study,³⁵ 20% of patients developed vascular compromise after injection with HA in the glabellar region. However, this rate appears higher than usual and may be caused in part by the small sample size of the study ($n = 10$) and changes in current injection techniques and volumes used. In another retrospective analysis of 139 patients, 40 patients reported adverse events, 10 of whom were injected with HA and 5 with PLLA. The most common adverse reaction was nodule/hardening in 80% of patients injected with PLLA, followed by pain, pruritus, discoloration, erythema, and swelling in 20% of cases. No ulceration or abscess formation was noted. Patients injected with HA fillers primarily experienced site reactions, such as erythema, swelling, and pain³⁶ (Figs 1 and 2). A large systematic review of HA fillers that included 10 randomized, blinded clinical trials, 53 clinical reports, and several additional open-label and retrospective studies identified only 8 serious events of 4605 total patients, all of which were determined to be unrelated to filler injection.³⁷

In a recently published 5-year retrospective review of 2089 soft tissue filler injections,²³ CaHA was the filler most commonly associated with complications. This series consisted of 1047 HA, 811 PLLA, and



Fig 2. A 51-year-old woman who developed prolonged erythema and edema from hyaluronic acid filler placed in the nasolabial folds.

231 CaHA injections. The complications arising from CaHA injections included cellulitis in 3 patients, submucosal nodule formation in 1 patient, and 1 case of partial thickness alar necrosis after nasolabial fold injections. Five patients treated with PLLA developed subcutaneous nodules. HA injections were least likely associated with complications. One patient treated with HA developed an inflammatory granuloma after lip augmentation.²³

LASERS, LIGHT, AND RADIOFREQUENCY DEVICE SAFETY

Key points

- Many organizations regulate laser operations in the United States, but these regulations are not strictly enforced
- The most frequently used regulatory document that provides guidance for the safe use of lasers in medicine is the American National Standards Institute document Z136.3
- Laser safety includes the use of protective eyewear, laser signage, control of surgical smoke, tissue splatter and plume, and attention to nonbeam and beam hazards
- Cutaneous injuries are the most frequent complications, with laser hair removal being the most common procedure resulting in litigation

In the United States, laser standards and regulations are not strictly enforced. In fact, only 12 states have laser regulations.³⁸ The requirements entail registration of lasers and the licensing of individual operations and institution, but physician-used medical lasers are exempt from these regulations. The national organizations that regulate laser operations are the American National Standards Institute (ANSI), the Center for Devices and Radiological Health (CDRH) of the FDA, the Department of Labor's Occupational Safety and Health Administration

(OSHA), and the Council of Radiation Control Program Directors (CRCPD).³⁸ The ANSI Z136.3 is a regulatory document on laser safety most frequently used in health care environments that provides guidance for the safe use of lasers in medicine. Standards are implied, but there is no requirement for adherence; compliance is voluntary unless specifically mandated by an institution or organization. In addition, OSHA does not have a comprehensive laser standard. The only construction standard states “employees whose occupation or assignment requires exposure to laser beams shall be furnished suitable laser safety goggles which will protect for the specific wavelength of the laser and be of the optical density adequate for the energy involved.” Studies have shown that 70% of all laser accidents to operators result from inappropriate or absent use of protective eyewear. Ocular complications have resulted from both direct and indirect exposure; laser energy can be reflected. Types of ocular injuries are wavelength specific. The degree of ocular damage is dependent on the laser irradiance, exposure time, and beam size.³⁹ Therefore, laser-protective eyewear is a well-recognized precaution, and includes wrap-around glasses and goggles, which are rated by optical density (OD) at various wavelengths. An OD of ≥ 4 at the particular wavelength of laser used is considered safe for dermatologic lasers.

A common misconception among laser users is that laser safety consists of the use of protective eyewear and signage of laser use only. National audits have revealed many misconceptions with laser safety, noncompliance, unsafe practices, and potential medicolegal issues. For example, plume and tissue splatter are potential safety issues that may be overlooked. The Centers for Disease Control and Prevention, OSHA, and state regulations have recognized the hazards of surgical smoke and have developed recommendations for its control. Particulates as small as $0.12\text{ }\mu\text{m}$, which include bacteria, human papillomavirus/HIV, carbon, and live cellular particles have been identified in surgical smoke.⁴⁰ Human papillomavirus has been cultured from plume generated by the CO₂ laser treatment of warts. The use of smoke evacuators, gloves, masks, and filters are important precautions. Tissue splatter is another potential hazard that may occur with Q-switched lasers. Other types of nonbeam hazards include fire and electrical hazards associated with high-voltage lasers. It is important to always be aware of the surgical or room setting, and special care must be taken to avoid exposure of flammable objects or liquids and drapes to the laser beam.

Cutaneous injuries are the most frequent complications and the most common cause for legal action



Fig 3. A 65-year-old woman who underwent intense pulsed-light treatment that resulted in a scar on the right upper lip.



Fig 4. A 42-year-old woman with glabellar necrosis after the use of a hyaluronic acid filler.

in laser surgery. A recent study investigated legal claims between 1985 and 2012 related to cutaneous laser surgery; 174 laser-induced injury lawsuits were found.⁴¹ The most common procedure that resulted in litigation was laser hair removal ($n = 63$). This may be because laser hair removal is the most frequent laser procedure and not necessarily because it has a high complication rate. The second most commonly litigated procedure was rejuvenation ($n = 43$). This includes conventional CO₂ resurfacing, which has fallen largely out of favor, ablative and nonablative fractional resurfacing, and intense pulsed-light treatments. Vascular and leg vein treatments represented 8% and 7.5% of lawsuits, respectively. The most common injuries included burns (47%), scars (38.8%), and pigmentation (23.5%). Four eye injuries and 2 deaths have been reported⁴¹ (Figs 3–6).

Common errors in cutaneous injuries associated with laser and light devices include improper laser



Fig 5. A 58-year-old woman who underwent ablative laser treatment and subsequently developed a candidal infection.



Fig 6. A 45-year-old woman with a depressed scar caused by a burn sustained by intense pulsed-light therapy.

selection. In selecting a laser/light device for a treatment, it is important to consider the target chromophore but also the skin type of the patient. In treating patients with dark skin types, the use of longer wavelengths or higher cutoff filters as well as longer pulse durations and lower fluences are recommended. Appropriate precooling, cooling during the procedure, and postcooling should also be considered to provide an extra measure of epidermal protection. In addition, a detailed disclosure of potential side effects protects not only the patient but also the provider.

The risk of scarring is low with pigment-specific, vascular, and nonablative lasers. Resurfacing lasers, such as the erbium and CO₂, carry the greatest risk of scarring because of dermal destruction and a higher risk of infection, which can ultimately lead to scarring. The advent of fractional lasers has minimized this complication.

The CO₂ laser is particularly hazardous because its wavelength in the far infrared and invisible spectrum is not visible; injuries and hazards may go unnoticed. The neodymium-doped yttrium aluminium garnet (Nd:YAG) laser should be approached with even greater caution, because it penetrates deeply because of its wavelength and is also invisible.



Fig 7. A 55-year-old woman who developed a coloboma caused by ocular injury secondary to the use of inappropriate safety eyewear.

There have been several reports of serious retinal injuries with Nd:YAG lasers.^{42,43} (Fig 7).

Radiofrequency energy has been used medically for years, but more recently has been applied cosmetically in tightening devices and in fractional ablative devices. These devices are billed as “sublative rejuvenation” in that they deliver energy focally to the dermis and spare the epidermis. This focused energy delivery preserves the epidermis and translates to fewer complications, especially in patients with darker skin types.⁴⁴ Contraindications to radiofrequency devices include implantable medical devices, such as pacemakers and defibrillators, and active dermatologic conditions, including collagen vascular and autoimmune diseases. Device companies recommend avoiding treatment over areas of skin marked with tattoos and caution against use on areas of the body that may contain metal implants, hardware, and braces.

In this era of cosmetic dermatology and diversity of laser operators, it is important to ensure that all staff handling and operating lasers are well trained and supervised to minimize the risk of injury.

COMPLICATIONS AND LEGAL ISSUES ARISING WITH COSMETIC EXTENDERS

Key points

- **Lawsuits involving laser devices are commonly due to non-physician operators, however the supervising physician is commonly the defendant.**
- **Proper training and supervision is essential**

The original role of physician extenders was to expand primary care in underserved regions. The passage of the Balanced Budget Act in 1997 enabled independent billing and payment to NPs and PAs. Subsequently, the number and role of physician extenders in dermatology has expanded greatly.

When mid-level providers are supervised by a physician, they bill at and are reimbursed 100% of the contracted Medicare rate. When billing independently, MLPs are reimbursed at 85% of the contracted rate. In a 2012 analysis of NP and PA billing there were over four million procedures billed independently by NPs and PAs, with over half of these representing dermatology codes.⁴⁵ Expanding this analysis to cosmetic procedures, a study of legal action in laser surgery identified 174 cases between 1985 and 2012. Of these cases a non-physician laser operator performed 40%, and though the physician operated the laser in only 57.5% of these suits, they were named defendants in 73.8% of these cases. State laws that assign liability to the supervising physicians explain this disparity. In addition, many mid-level providers do not carry malpractice insurance and naming the insured physician as a defendant increases the likelihood of a successful payment in a lawsuit.⁴¹ In 2014, the same authors performed another analysis of litigation related to laser surgery. They found an increase in cases involving a non-physician operator from 36.3% in 2008 to 77.8% in 2011. Laser hair removal was the most commonly litigated procedure. Interestingly, though non-physicians perform only one-third of laser hair removal procedures, this group represented 85.7% of hair removal lawsuits. Of these, 64% were performed outside a traditional medical setting, indicating that supervision by a physician may ameliorate some of this risk.^{46,47}

One of the most feared complications of laser surgery regards pigmented lesions and melanoma. There have been several reports of melanoma diagnoses relating to laser treatment, though it is unknown whether these cases are caused by laser energy, or, as is more commonly suggested, misdiagnosed as benign lesions prior to laser treatment. One report is of a patient who paid 10 Euro for treatment of pigmented lesions at a laser spa in Japan, and was later diagnosed with metastatic melanoma with a large focus at the site of laser treatment.⁴⁸ Accurate diagnosis of pigmented lesions is challenging, even for seasoned dermatologists, and there are several case reports of patients who presented for laser removal of lesions that were caught and diagnosed as melanoma by dermatologists.⁴⁹ These studies suggest that the judgment of a well-trained dermatologist is vital to patient safety prior to laser treatment of pigmented lesions.

A German study conducted in 2013 investigated the most frequent errors resulting from the use of laser or IPL devices by unsupervised medical laypeople (tattooists, cosmetologists, etc). This

survey identified 50 patients who reported complications. The most reported complications were pigmentation changes in 81% of patients, scarring in 25% of patients, textural changes in 14%, and inadequate treatment in 5% of patients.⁵⁰ The sources of error included excessive energy application in 63% of cases, improper laser selection in 40%, inappropriate use of laser on skin type in 21% of cases, inadequate cooling in 7%, and inadequate information to patients in 5% of cases.

In a field like dermatology, where vast numbers of procedures are performed, complications are inevitable. Physician extension is becoming more common in our field and as studies have demonstrated, physicians who supervise extenders are often held liable when complications arise. It is imperative that all laser operators be properly trained and closely supervised to protect the patient from injury, increase efficacy, and avoid legal pitfalls.

REFERENCES

1. Tierney EP, Hanke CW. Recent trends in cosmetic and surgical procedure volumes in dermatologic surgery. *Dermatol Surg.* 2009;35:1324-1333.
2. Ahn CS, Davis SA, Dabade TS, Williford PM, Feldman SR. Cosmetic procedures performed in the United States: a 16-year analysis. *Dermatol Surg.* 2013;39:1351-1359.
3. American Society for Aesthetic Plastic Surgery. Statistics. Available from: <http://www.surgery.org/media/statistics>. Accessed November 16, 2014.
4. Korman JB, Jalian HR, Avram MM. Analysis of botulinum toxin products and litigation in the United States. *Dermatol Surg.* 2013;39:1587-1591.
5. Vartanian AJ, Dayan SH. Complications of botulinum toxin A use in facial rejuvenation. *Facial Plast Surg Clin North Am.* 2005;13:1-10.
6. Carruthers JA, Lowe NJ, Menter MA, et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol.* 2002; 46:840-849.
7. Matarasso SL, Matarasso A. Treatment guidelines for botulinum toxin type A for the periocular region and partial upper lip ptosis following injections to the lateral canthal rhytids. *Plast Reconstr Surg.* 2001;108:208-214.
8. Brin MF, Boodhoo TI, Pogoda JM, et al. Safety and tolerability of onabotulinumtoxinA in the treatment of facial lines: a meta-analysis of individual patient data from global clinical registration studies in 1678 participants. *J Am Acad Dermatol.* 2009;61:961-970.
9. Rubin MG, Dover JS, Glogau RG, Goldberg DJ, Goldman MP, Schlessinger J. The efficacy and safety of a new US botulinum toxin type A in the retreatment of glabellar lines following open-label treatment. *J Drugs Dermatol.* 2009;8: 439-444.
10. Kane MAC, Brandt F, Rohric RJ, et al. Evaluation of variable-dose treatment with a new US botulinum toxin type A (Dysport) for correction of moderate to severe glabellar lines: results from a phase 3, randomized, double-blind, placebo-controlled study. *Plast Reconstr Surg.* 2009;124:1619-1629.

11. Lee JH, Park JH, Lee SK, et al. Efficacy and safety of incobotulinum toxin A in periocular rhytides and masseteric hypertrophy: side-by-side comparison with onabotulinum toxin A. *J Dermatolog Treat.* 2014;25:326-330.
12. Carruthers A, Carruthers J, Heinz M, et al. Multicenter, randomized phase III study of a single dose of incobotulinumtoxinA, free from complexing proteins, in the treatment of glabellar frown lines. *Dermatol Surg.* 2013;39:551-558.
13. Hanke CW, Narins RS, Heinz M, et al. IncobotulinumtoxinA, a botulinum toxin free from complexing proteins, in the treatment of glabellar frown lines. *Dermatol Surg.* 2013;39:891-899.
14. Cote TR, Mohan AK, Polder JA, et al. Botulinum toxin type A injections: adverse effects reported to the US Food and Drug Administration in therapeutic and cosmetic cases. *J Am Acad Dermatol.* 2005;53:407-415.
15. Lemperle G, Gauthier-Hazan N, Wolters M, Eisemann-Klein M, Zimmermann U, Duffy DM. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. *Plast Reconstr Surg.* 2008;123:1864-1873.
16. Pavicic T. Calcium hydroxylapatite filler: an overview of safety and tolerability. *J Drugs Dermatol.* 2013;12:996-1002.
17. Sadick NS, Katz BE, Roy D. A multicenter, 36-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. *Dermatol Surg.* 2007;33(suppl 2):S122-S126.
18. Lafaille P, Benedetto A. Fillers: contraindications, side effects and precautions. *J Cutan Aesthet Surg.* 2010;3:16-19.
19. Cosatti M, Fernández Romero DS, Juri MC, Malbran A. Facial angioedema after filler injections. Description of five cases [in Spanish]. *Medicina (B Aires).* 2010;70:513-517.
20. Sclafani AP, Fagien S. Treatment of injectable soft tissue filler complications. *Dermatol Surg.* 2009;35:1672-1680.
21. McCleve DE, Goldstein JC. Blindness secondary to injections in the nose, mouth, and face: cause and prevention. *Ear Nose Throat J.* 1995;74:182-188.
22. Grunebaum LD, Alleman IB, Dayan S, Mandy S, Baumann L. The risk of alar necrosis with dermal fillers. *Dermatol Surg.* 2009;35:1635-1640.
23. Daines SM, Williams EF. Complications associated with injectable soft-tissue fillers: a 5-year retrospective review. *JAMA Facial Plast Surg.* 2013;15:226-231.
24. Werschler P, Cosmetic Study Investigator Group. Efficacy of injectable poly-L-lactic acid versus human collagen for the correction of nasolabial fold wrinkles. Presented at the American Society for Dermatologic Surgery, Palm Desert, CA, October 28, 2006. Abstract CS359.
25. Narins RS, Baumann L, Brandt FS, et al. A randomized study of the efficacy and safety of injectable poly-L-lactic acid versus human-based collagen implant in the treatment of nasolabial fold wrinkles. *J Am Acad Dermatol.* 2010;62:448-462.
26. Moyle GJ, Lysakova L, Brown S, et al. A randomized open label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. *HIV Med.* 2004;5:82-87.
27. Moyle GJ, Brown S, Lysakova L, Barton SE. Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV related facial lipoatrophy. *HIV Med.* 2006;7:181-185.
28. Brown SA, Rohrich RJ, Baumann L, et al. Subject globale evaluation and subject satisfaction using injectable poly-L-lactic acid versus human collagen for the correction of nasolabial fold wrinkles. *Plast Reconstr Surg.* 2011;127:1684-1692.
29. Weinkle S. Minimizing the risk of adverse events with injectable poly-L-lactic acid. *Int J Dermatol.* 2007;6:2. Accessed March 20, 2014.
30. Valantin MA, Aubron-Olivier C, Ghosn J, et al. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *Aids.* 2003;17:2471-2477.
31. Vleggaar D. Soft-tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg.* 2006;118(3 suppl):46S-54S.
32. Borelli C, Kunte C, Weisenseel P, Thoma-Greber E, Korting HC, Konz B. Deep subcutaneous application of poly-L-lactic acid as a filler for facial lipoatrophy in HIV-infected patients. *Skin Pharmacol Physiol.* 2005;18:273-278.
33. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol.* 2005;52:233-239.
34. Glaich AS, Cohen JL, Goldberg LH. Injection necrosis of the glabella: protocol for prevention and treatment after use of dermal fillers. *Dermatol Surg.* 2006;32:276-281.
35. Wolber L, Zielke H, Wiest L, Rzany B. Adverse reactions to injectable filler substances in aesthetic dermatology—results of the Injectable Filler Safety Study. *J Invest Dermatol.* 2005;125:855.
36. Bachmann F, Erdmann R, Hartmann V, Weist L, Rzany B. The spectrum of adverse reactions after treatment with injectable fillers in the glabellar regions: results from the Injectable Filler Safety Study. *Dermatol Surg.* 2009;1629-1634.
37. Cohen JL, Dayan SH, Brandt FS, et al. Systematic review of clinical trials of small- and large-gel-particle hyaluronic acid injectable fillers for the aesthetic soft tissue augmentation. *Dermatol Surg.* 2013;39:205-231.
38. US Department of Labor, Occupational Safety and Health Administration website. OSHA Technical Manual, Section III, Chapter 6. Available at: https://www.osha.gov/dts/osta/otm_iii/otm_iii_6.html. Accessed November 16, 2014.
39. Bader O, Lui H. Laser safety and the eye: hidden hazards and practical pearls. Poster presented at the American Academy of Dermatology Annual Meeting, 1996.
40. Smalley PJ. Laser safety: beyond signs and goggles. *The Dermatologist.* 2008;12:7.
41. Jalian HR, Jalian CA, Avram MM. Common causes of injury and legal action in laser surgery. *JAMA Dermatol.* 2013;149:188-193.
42. Sliney DH, Trokel SL. *Medical lasers and their safe use.* New York: Springer-Verlag; 1992.
43. Sliney DH, Wolbarsht ML. *Safety with lasers and other optical sources: a comprehensive handbook.* New York: Plenum Press; 1980.
44. Rongsaard N, Rummaneethorn P. Comparison of a fractional bipolar radiofrequency device and a fractional erbium-doped glass 1,550-nm device for the treatment of atrophic acne scars: a randomized split-face clinical study. *Dermatol Surg.* 2014;40:14-21.
45. Coldiron B, Ratnarathorn M. Scope of physician procedures independently billed by mid-level providers in the office setting. *JAMA Dermatol.* 2014;150:1153-1159.
46. Jalian HR, Jalian CA, Avram MM. Increased risk of litigation associated with laser surgery by nonphysician operators. *JAMA Dermatol.* 2014;150:407-411.

47. Jalian HR, Avram MM. Mid-level practitioners in dermatology: a need for further study and oversight. *JAMA Dermatol*. 2014; 150:1149-1151.
48. Larsen TH, Nielsen M, Lindskov R, Hegelund BL, Haedersdal M. Metastases from malignant melanoma after laser treatment of undiagnosed pigmented skin lesions. *Lasers Med Sci*. 2013;28:1403-1404.
49. Stankiewicz K, Chuang G, Avram M. Lentigines, laser and melanoma: a case series and discussion. *Lasers Surg Med*. 2012;44:112-116.
50. Hammes S, Karsal S, Metelmann HR, et al. Treatment errors resulting from the use of laser and IPL by medical laypersons: results of a nationwide survey. *J Dtsch Dermatol Ges*. 2013;11: 149-156.

Melanoma in situ

Part I. Epidemiology, screening, and clinical features

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Learning objectives

Describe the current epidemiologic trends in MIS, the role of screening, and the evidence on prevention.

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The incidence of melanoma has steadily increased over the past 3 decades, with melanoma in situ comprising a disproportionately high percentage of the rising incidence. Our understanding of melanoma in situ has been shaped by epidemiologic and clinical studies. Central to a review of melanoma in situ is a focus on its epidemiology, pathology, biologic behavior, treatment, and clinical outcome, which may differ significantly from that of malignant melanoma. Part I of this continuing medical education article reviews the epidemiology, risk factors, and clinical features of melanoma in situ; part II covers the histopathology, treatment options, and clinical management. (J Am Acad Dermatol 2015;73:181-90.)

Key words: lentigo maligna; melanoma; melanoma in situ.

The incidence of melanoma has steadily increased over the past 3 decades, with melanoma in situ (MIS) comprising a disproportionately high percentage of the rising incidence.¹⁻⁴ According to the American Joint Committee on Cancer, MIS is defined as melanomas that are limited to the epidermis.⁵ Lentigo maligna is a subtype of MIS, and is defined histologically when atypical melanocytes are present in the basal layer with a background of solar elastosis. Comparatively,

Abbreviations used:

MIS:	melanoma in situ
MM:	malignant melanoma
PPV:	positive predictive value
SCREEN:	Skin Cancer Research to provide Evidence for Effectiveness of Screening in Northern Germany
SEER:	Surveillance, Epidemiology, and End Results
SPF:	sun protective factor

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invasive melanomas represent tumors that have invaded the dermis. The combined incidence of MIS and invasive melanoma has been increasing by 2.6% annually over the last decade, with MIS constituting the majority of this increase.⁶ MIS has increased 9.5% annually, representing one of the fastest growing malignancies in the Surveillance, Epidemiology, and End Results (SEER) database.⁷ Some clinicians question whether this is a true increase in tumor burden or a result of overdiagnosis of MIS because of its complex histopathologic nuance. Increased rates of obtaining a skin biopsy specimen between 1968 and 2001 were also associated with an increased incidence of melanoma during the same time period, further fueling this controversy.⁸⁻¹⁰

MIS is considered stage 0 and as such has no associated direct mortality. However, there is an association with an increased risk of developing second primary tumors.^{5,11-14} Specifically, patients with MIS are at much higher risk of developing a subsequent primary malignant melanoma (MM), leading dermatologists to recommend regular screening of patients with pigmented lesions.^{13,15,16} Despite these recommendations, the evidence for early detection through screening and prevention of MIS by sun avoidance and protection strategies is indeterminate, in part because of the difficulty of performing controlled trials. In order for screening to be a successful tool, physicians must be able to accurately diagnose MIS based on a clinical examination. These tumors can be challenging to distinguish from benign pigmented lesions, especially in sun-exposed areas. The use of dermoscopy may be a helpful tool in the diagnosis of MIS, although biopsy is always required for definitive diagnosis.

We review the epidemiologic evidence for an increase in the incidence of MIS and address the controversy about whether there is in fact a true increase in incidence or simply an overdiagnosis of MIS. We discuss the increased risk of secondary tumors after a diagnosis of MIS and the studies examining the effect of screening and sunscreen usage. A significant limitation in this review is that much of the literature addresses MM, and not MIS. Therefore, a major assumption is made when applying the findings of these studies on screening and sunscreen use to MIS. Clinical and dermoscopic features of MIS will also be reviewed, highlighting differences between benign nevi, MIS, and MM.

INCIDENCE

Key points

- The incidence of melanoma in situ has been increasing steadily over the past decade,

with a faster rate of increase in younger patients (20-49 years of age) than older patients and in men compared to women

- **The annual percentage change in incidence is the highest of any tumor in the Surveillance, Epidemiology, and End Results database**

An increase in the incidence of cutaneous melanoma (MIS and MM) over the past 3 decades is well documented.¹⁷ In Europe, Australia (Queensland), and the United States, MIS makes up a disproportionate amount of the annual increase in melanoma.¹⁸⁻²⁰ In Queensland, the incidence of MIS between 1982 and 2002 increased at a rate of 10.6% for men and 8.5% for women, whereas invasive melanoma increased at a rate of 2.6% for men and 1.2% for women.²¹ In the United States, the incidence of MIS has risen from <1 case per 100,000 patients in 1973 to 14 cases per 100,000 patients in 2006.¹¹ This rapid increase amounts to an annual percent change of 9.5%, which is higher than that of invasive melanomas (annual percent change over the past decade, 2.6%).¹¹ The annual percent change of MIS is the highest of any tumor recorded by the SEER database, which indexes leukemia, bladder, breast, colon, endometrial, renal, lung, pancreatic, prostate, and thyroid cancers, and non-Hodgkin's lymphoma.⁷ Younger patients (20-49 years of age) have a faster rate of increase for MIS than older patients.⁷ Men are also more commonly diagnosed with MIS than women (men, 55.7%; women, 44.3%). The mean age of those diagnosed with MIS was 61.2 years, with whites making up 93.1% of the affected population. Comparatively, the mean age of patients diagnosed with MM is 54 years; men make up 53.4% of this population.²² Fig 1 shows locations of MIS, with head and neck being the most common location. In contrast, head and neck is the fourth most common location of MM (18.2%) after the trunk (32%), upper extremities (23.4%), and lower extremities (20.3%).^{7,22} Fig 2 shows subtypes of MIS, as categorized by the SEER study.⁷ The rapid increase in the incidence of MIS—if real and not related to overdiagnosis—warrants public health efforts to address the disease. Such steps are predicated on understanding the basis of the increase.

CONTROVERSY ABOUT INCIDENCE

Key points

- There is controversy about whether there is in fact a true increase in incidence or simply an increase in diagnosis of melanoma in situ

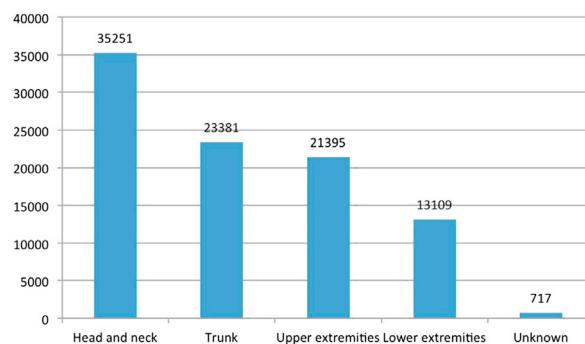


Fig 1. Locations of melanoma in situ recorded by the Surveillance, Epidemiology, and End Results study between 1973 and 2006. Total numbers of melanoma in situ in each area shown.⁷

- Improved screening, increased reporting, or changes in histologic criteria may be the cause of increased diagnosis and the apparent increase in incidence

Because of the growing incidence of MIS, some clinicians have raised questions about whether there is indeed an epidemic of increased tumor burden or whether it represents an apparent increase related to improved screening and reporting or changes in histologic criteria. Welch et al¹⁰ conducted a population-based study of the SEER-Medicare linked data and found a 2.5-fold increase in biopsy rates in the Medicare population between 1986 and 2001. Over the same time period, the incidence of MM also had a 2.4-fold increase, suggesting an association between increased biopsy rates and invasive melanoma diagnosis. For MIS, each 1000 biopsy specimens were estimated to result in 4.4 diagnoses of MIS.¹⁰ Studies exploring the incidence of MM based on tumor thickness and demographic factors have suggested that increased screening and biopsy alone cannot account for the dramatic increase in the incidence of this tumor, especially because incidence increased without regard to socioeconomic status, which functioned as a surrogate marker for access to care and screening.^{8,23} In addition, others have suggested that the increase in incidence of MIS is related to a general trend toward overdiagnosing melanocytic lesions as malignant. In 1 study, slides that were previously diagnosed as dysplastic nevi and radial growth phase melanoma between 1988 and 1990 were reevaluated by dermatopathologists in 2008 and 2009. Diagnoses rendered in 1988 to 1990 resulted in a mean number of 11 melanomas; diagnoses of the same slides rendered in 2008 to 2009 resulted in a mean number of 18 melanomas.²⁴

These studies did not address MIS specifically, which makes it difficult to interpret whether the

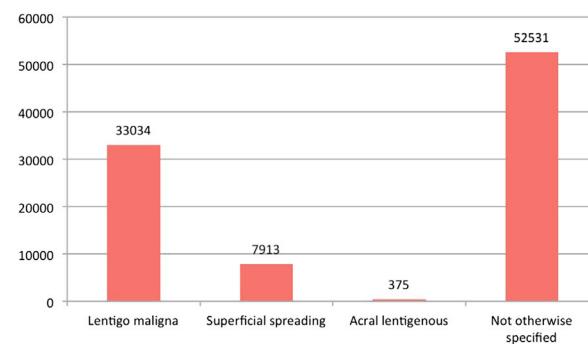


Fig 2. Pathology of melanoma in situ recorded by the Surveillance, Epidemiology, and End Results study between 1973 and 2006.

incidence of MIS is truly increasing or whether it is a reflection of increased diagnostic scrutiny (ie, more vigilant biopsy and screening efforts and more aggressive interpretation by dermatopathologists).

RISK OF SECONDARY TUMORS AND MORTALITY

Key points

- Patients diagnosed with melanoma in situ have a higher risk of developing secondary tumors
- Malignant melanoma (a second primary) is the most common secondary tumor diagnosed
- Patients with melanoma in situ have the same life expectancy as the general population

Similar to MM, MIS is associated with a higher risk of developing secondary tumors (standardized incidence ratio [SIR], 1.2 [95% confidence interval {CI}, 1.2-1.3]), especially MM (SIR, 8.1 [95% CI, 7.7-8.6]).^{11,22} Other secondary tumors diagnosed after MIS included tumors of the lip (SIR, 1.7 [95% CI, 1.1-2.6]), lymphocytic leukemia (SIR, 1.6 [95% CI, 1.3-2]), non-Hodgkin's lymphoma (SIR, 1.2 [95% CI, 1-1.4]), and hematologic tumors (SIR, 1.1 [95% CI, 1-1.3]).¹¹ A lower risk of malignancy was found for tumors of the digestive system (SIR, 0.8 [95% CI, 0.7-0.8]), colon/rectum/anus (SIR, 0.8 [95% CI, 0.7-0.9]), pancreas (SIR, 0.8 [95% CI, 0.6-0.9]), liver/gallbladder/biliary ducts (SIR, 0.7 [95% CI, 0.5-0.9]), respiratory system (SIR, 0.7 [95% CI, 0.6-0.7]), lung/bronchus (SIR, 0.7 [95% CI, 0.6-0.7]), and larynx (SIR, 0.4 [95% CI, 0.2-0.7]).¹¹ The mean time to diagnosis of a second tumor of any type was 14 years. While additional evaluation is needed, this association could reflect genetic or environmental factors that predispose individuals diagnosed with

MIS to developing additional malignancies or even decrease the likelihood of others.¹¹

Patients with MIS have the same life expectancy as the general population. In contrast, the 5-year mortality of patients with MM is higher than that of the general population, although this trend has been improving over the past 3 decades.⁷

SCREENING RECOMMENDATIONS

Key points

- There is limited evidence to support the usefulness of full body skin examinations in screening for melanoma *in situ* by primary care physicians
- Some evidence suggests that screening for melanoma *in situ* by dermatologists may be beneficial, particularly in higher-risk populations

The issue of the value of screening for MIS is complicated by the fact that most studies either focused on MM or, if MIS was included, it was not distinguished from MM. Nonetheless, it is reasonable to conclude that guidance regarding screening practices and outcomes for MM would be applicable to the clinical aspects of screening diagnosis if not to alterations in patient mortality. Currently, the United States Preventative Task Force (USPTF) reports limited evidence to support the utility of full body skin examinations in screening for melanoma/skin cancer by primary care physicians.^{25,26} As such, it is silent on the usefulness of full body skin examinations in the asymptomatic patient without specific risk factors. This recommendation, published in 2009, was based on an English-language search of relevant articles examining the evidence for and against full body skin examinations.^{25,26} Before this 2009 recommendation, the 2001 USPTF report also reported limited evidence to recommend for or against skin screening in asymptomatic individuals. Both reports specifically point out 2 practice gaps, including the lack of quality evidence demonstrating improved outcomes with screening and the lack of information about a primary care physician's ability to perform full body skin examinations in a regular office visit.^{25,26} There are substantial challenges to conducting a screening study that seeks to ascertain a benefit to screening.

Importantly, these recommendations do not address screening by specialists (ie, dermatologists, specialty midlevel providers). In addition, these recommendations specifically apply to the general adult population with an average risk of skin cancer

and may not pertain to those with an already established history of skin cancer or those with a higher risk than the general public.^{25,26}

Because most studies do not distinguish MIS from MM, the closest approximation to analyzing the value of screening is derived from large prospective studies of population screening for melanoma. The Skin Cancer Research to provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) project was a population-wide skin cancer screening study using both primary care physicians and dermatologists. In this study, residents in the German state of Schleswig-Holstein received full body skin examinations and those in the state of Saarland did not. Based on comparisons between MIS incidence before, during, and after the full body skin examination intervention, the population receiving skin examinations showed an increase in the incidence of MIS, with the greatest differences noted in women. After the conclusion of the study intervention, MIS incidence decreased in women. The SCREEN study was one of the first to show the impact that screening can have on improved MIS diagnosis.^{27,28}

The incidence of nonmelanoma skin cancer also increased during the screening intervention period of the SCREEN study. Specifically, incidence rates increased from 81.5 per 100,000 people to 111.5 per 100,000 people during the screening period. Therefore, increased screening of melanoma also results in increased detection of nonmelanoma skin cancer and related morbidity and health care costs.²⁹ In the SCREEN study, 1 in 23 individuals receiving full body skin examinations underwent excision for treatment of malignant skin tumors.³⁰

Other studies have examined the positive predictive value (PPV) for the diagnosis of melanoma through screening by both general practitioners and dermatologists. One of the reasonable conclusions that can be drawn from the literature is that MIS can be diagnosed in a fashion similar to invasive MM. The remaining issue is whether early diagnosis of MIS has any impact on morbidity. One Australian study examined community-based general practitioners conducting full body skin examinations. Of 16,383 skin examinations conducted, 2302 patients were referred for suspicious lesions. The specificity of finding a lesion histologically confirmed as melanoma was 86.1%, with a 2.5% PPV. The specificity of detecting melanoma in patients ≥ 50 years of age was comparable to the specificity of mammography in this high-risk Australian population.²⁰ Other studies conducted in the late 1990s found PPVs ranging from 6% to 24%. Higher

PPVs were associated with general practitioners that had previously received some type of training as part of the study.^{31,32} When screening for melanoma was performed by a plastic surgeon or dermatologist in Australia, the PPV was found to be approximately 10%, with a specificity of 95% to 99% and a sensitivity of 64% to 82%.³³ In the United States, participants who self-selected for skin cancer screening were also studied in the late 1990s. Of 132 patients, the PPV for melanoma ranged from 6% to 15%. A major limitation to this study was the diagnosis of only 2 melanomas in this population.³² Other screening studies conducted during this time found similar PPVs for melanoma in self-selecting populations.³⁴⁻³⁶ An analysis of the American Academy of Dermatology's screening program in the 1990s found a PPV of 11% for melanoma. When this population was restricted to patients ≥ 50 years of age, the PPV rose to 21%.³⁷⁻³⁹

The age at which to begin screening is unclear. Because there are few studies examining the impact of screening on MIS, it is hard to extrapolate from their data what the target age group for screening should encompass. Based on SEER incidence data, MIS is increasing at a faster rate in younger patients (ie, those 20-49 years of age), although the mean age of those diagnosed with MIS is still 61.2 years.⁷ Screening should ideally encompass both of these age groups.

When considering the benefits of screening for MIS and its potential impact on morbidity, the harms of screening are also worth considering. Namely, the number needed to screen for melanoma is estimated to be 25,000 patients to prevent 1 melanoma-related mortality.⁴⁰ When examining the number needed to screen for detection of melanoma, this number drops to 1 in 620, based on data from the SCREEN study.²⁷ These numbers apply to a calculation for all melanomas, including MIS and MM. Therefore, the cost and burden of screening for MIS may differ significantly.

SUNSCREEN USE

Key points

- Sunscreen use has been shown to prevent invasive melanoma in some studies
- It is unknown whether sunscreen is effective in specifically preventing melanoma in situ

Sunscreen use can prevent or mitigate sunburn by reducing the impact of ultraviolet radiation on the skin. Laboratory studies on animal models confirm this role for sunscreens.⁴¹ Sunscreens are one of the most common forms of sun protection used by the general public, although its application

is frequently suboptimal.⁴²⁻⁴⁴ The sun protective factor (SPF) is tested at an application thickness on the skin surface of 2 mg/cm^2 . Several studies have shown that users routinely apply an inadequate amount of sunscreen, ranging from 0.3 to 1 mg/cm^2 . This thin application considerably decreases the amount of ultraviolet protection afforded by the sunscreen.⁴⁵ The use of high SPF (≥ 70) compositions with frequent reapplication or double-layered applications may compensate for thin or uneven applications.^{46,47}

Because sun exposure is considered a major risk factor for melanoma, the use of sunscreen can theoretically decrease the incidence of melanoma. A randomized trial of sunscreens in children noted reductions in the development of melanocytic nevi, a strong predictor of melanoma. This effect was strongest in children with freckles. However, these studies did not investigate the effects on MIS and MM.^{48,49}

Evidence for the use of sunscreen in prevention of melanoma is sparse, with few randomized controlled trials. Data from case control studies have produced conflicting results. Some studies demonstrated decreased melanoma risk with routine use of SPF 15+ sunscreen and other sun protection methods (eg, long-sleeved shirts, staying in the shade) while other studies showed no association.⁵⁰⁻⁵² A metaanalysis of 9067 patients from 11 case controlled studies showed a relative risk of 1.01, indicating a lack of association between sunscreen use and melanoma.⁵¹ Other studies have suggested that sunscreen use may actually increase a person's risk for melanoma because individuals using sunscreen have longer sun exposures.^{53,54} Before 2011, the lack of randomized controlled trials left the effect of sunscreen on melanoma unanswered.

In 2011, Green et al published data from a randomized skin cancer prevention trial investigating the effect of sunscreen use in a community in Queensland, Australia. This study of 1621 adults randomized individuals to the use of SPF 16 sunscreen. Experimental group subjects were asked to apply sunscreen to sun-exposed areas (ie, the head, neck, arms, and hands) daily, with reapplication after water exposure, long sun exposure, and heavy sweating. Control group subjects were asked to use sunscreen at their normal frequency, which could have included no use of sunscreen. During the 5-year trial period, compliance with sunscreen use was recorded based on the weight of sunscreen bottles returned and by surveys querying subjects' weekly use of sunscreen. Ten years after conclusion of the trial, a

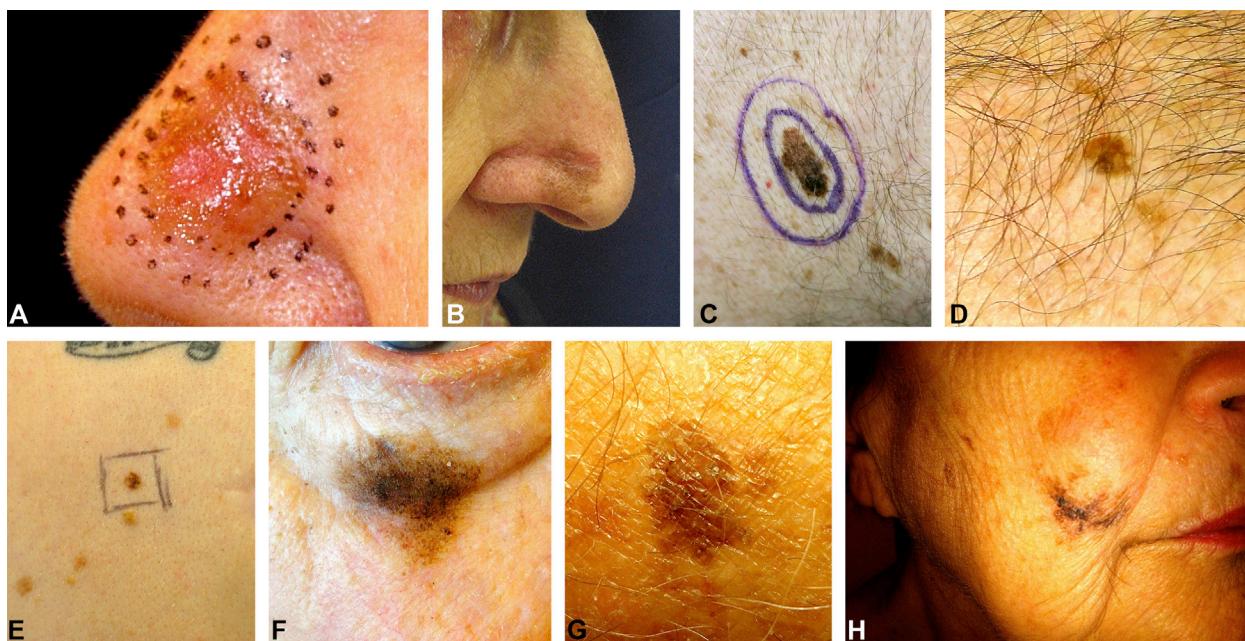


Fig 3. **A**, Melanoma in situ (MIS) >6 mm of the nose. **B**, Macular presentation of MIS. **C**, Variegate coloration of MIS; both brown and black portions are present. **D** and **E**, Superficial spreading melanoma variant of MIS. **F-H**, Lentigo maligna variant of MIS.

reduction in the number of melanomas diagnosed was observed in the trial group compared to control group, suggesting a preventative role for use of sunscreen in preventing invasive melanoma. Despite the reduction in invasive melanomas, it is notable that there were no significant differences between both groups with respect to MIS.⁵⁵ Therefore, the question of the efficacy of sunscreen use in prevention of MIS still remains. To the extent that the effect was not unequivocally answered, questions about the etiology or behavior of MIS may be raised.

While the evidence for sunscreen use in the prevention of MIS is indeterminate, dermatologists still often recommend use of these products to the general public. The other benefits of sunscreen, including reducing actinic keratoses, prevention of squamous cell carcinoma, and delay in appearance of sunburn-related erythema, warrant its use in at-risk populations.⁵⁶⁻⁶¹ In patients with a history of MM, there is an increase in sunscreen use immediately after diagnosis. Over time, this use becomes inconsistent and comparable to the use in those without a history of melanoma.⁶² These behavioral patterns may shed light on those patients diagnosed with MIS, although additional investigation is necessary to definitively assess sun-protective habits in those with a history of MIS.

CLINICAL FEATURES

Key points

- Melanoma in situ has clinical and dermoscopic features that may aid in its distinction from common nevi
- Lentigo maligna is considered by the World Health Organization as melanoma in situ

MIS can vary in size, shape, and color. In a study of 121 MIS lesions, 77% of lesions were >6 mm (Fig 3, A), 92% were macular (Fig 3, B), and 75% were asymmetric (Figure 3, F-H). Although the border was irregular in the majority of lesions, it was not thought to be poorly defined. The most common color present in the tumor was black (48%), followed by brown (41%), tan (16%), grey (8%), and pink (3%). The majority of lesions (98%) had >1 color present in the lesion (Fig 3, C-E).⁶³ Amelanotic MIS presents as an erythematous macule or plaque and may initially be misdiagnosed as an inflammatory disorder.⁶⁴⁻⁶⁶

Lentigo maligna (LM) subtype typically occurs on chronically sun-exposed skin. LM can act as a precursor to LM melanoma (Fig 3, F-H). Roughly 5% of LMs progress to invasive melanoma.⁶⁷ LM occurs most commonly on the face of elderly individuals and has a predilection for the nose and cheek. This slow-growing lesion typically presents as an asymmetric, brown-black macule with

color variation and irregular borders. LM can be difficult to distinguish histologically from the atypical melanocytic hyperplasia seen in severely sun-damaged skin.⁶⁸ This distinction will be discussed in part II of this continuing medical education article.

Some advocate that the current concept of LM^{69,70} actually embodies 2 distinct histologic entities, with LM recognized as atypical melanocytic hyperplasia and MIS, LM type showing confluence and nesting of atypical melanocytes at various layers of the epidermis.^{68,71} Despite this controversy, most studies have not made this distinction. The World Health Organization and national registries, such as SEER, recognize LM and MIS as the same entity, allowing reporting of both under the category of MIS.⁷²

Dermoscopy can be used to clinically diagnose melanomas. While nevi, MIS, and MM have many overlapping features, certain characteristics can help to distinguish MIS. Compared to typical nevi, MIS frequently has an atypical pigment network involving >50% of the lesion or the presence of multiple different pigment networks. Grey-blue regression is also more commonly observed in MIS lesions.⁷³ The comparison between atypical nevi and MIS is more difficult, because both can share similar features. In a study of 38 MIS and 136 atypical nevi, no distinguishing features could be found between the 2 entities in terms of geometry, color, textures, and islands of color, such as a grey-blue veil.⁷⁴

MIS and MM share several common dermoscopic features, making these lesions difficult to distinguish. Light brown areas are more common in MIS; grey-blue veils are more common in MM. When blue areas are present in MIS, they are more likely to show a reticular grey-blue pattern, compared to a more disorganized pattern in MM. This reticular pattern can serve as a distinguishing characteristic of MIS.⁷⁵ The distribution of blue areas (center vs. periphery) is similar in MIS and MM. Pepperling, or scattered blue-gray granules within an area of hypopigmentation, can be seen in similar proportions in both types of lesions. Both types of lesions can have a combination of the aforementioned features.^{75,76}

When considering MIS only, 8 different dermoscopic subtypes have been proposed: reticular grey-blue, reticular, multicomponent, island, spitzoid, inverse network, net-blue globules, and globular. Of these, the reticular grey-blue is the most common.⁷⁷ Other studies have also suggested various dermoscopic features that may be helpful in distinguishing MIS from other pigmented lesions.

These include the dermoscopic island, a well-circumscribed area with a uniform dermoscopic pattern that differs from the rest of the lesion.⁷⁸ The “mushroom-cloud sign” and “mistletoe sign” have also been described. The “mushroom-cloud sign” consists of a hyperpigmented area extending in one direction. Once past the border, a faint stalk-like projection can be seen.⁷⁹ The “mistletoe sign” represents well-circumscribed areas with nonuniform structures resembling branching pseudopods. This pattern arises from reticular or homogenous background patterns, which are reminiscent of mistletoe.⁸⁰ When specifically examining the LM subtype of MIS, LM features hyperpigmented follicular openings, rhomboidal structures, and irregular pigmented perifollicular dots.^{81,82}

In conclusion, the incidence of MIS has been steadily rising over the past 3 decades, with little impact on mortality or life expectancy. There is controversy as to whether this rising incidence in MIS represents overdiagnosis related to better screening methods and more biopsies or if it represents a true increase in incidence. Given the risk of a second primary tumor after a diagnosis of MIS, this condition still warrants close surveillance. Full body skin examinations are currently not recommended by the USPTF in the general population. This group does not address screening recommendations in the high-risk population, such as those with a strong family history or those with a personal history of skin cancer. Sunscreen use can help to decrease the incidence of MM, although its effect on MIS may be minimal. This area of research has proven difficult due to the large sample sizes required to detect differences in MIS incidence. Part II of this continuing medical education article will explore treatment, surveillance tools, and genetic considerations.

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REFERENCES

1. Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. *Br J Dermatol.* 2014;170:11-19.
2. Garbe C, Leiter U. Melanoma epidemiology and trends. *Clin Dermatol.* 2009;27:3-9.
3. StatBite: Distribution of melanoma incidence and mortality by age, 2001-2005. *J Natl Cancer Inst.* 2008;100:1498.
4. Gribin AV, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. *J Plast Reconstr Aesthet Surg.* 2007;60:32-40.
5. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009;27:6199-6206.

6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013;63:11-30.
7. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2014 Sub (1973-2012) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission. Available at: www.seer.cancer.gov. Accessed May 12, 2015.
8. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. *J Invest Dermatol.* 2009;129:1666-1674.
9. Lee KC, Weinstock MA. Melanoma is up: are we up to this challenge? *J Invest Dermatol.* 2009;129:1604-1606.
10. Welch HG, Woloshin S, Schwartz LM. Skin biopsy rates and incidence of melanoma: population based ecological study. *BMJ.* 2005;331:481.
11. Mocellin S, Nitti D. Cutaneous melanoma in situ: translational evidence from a large population-based study. *Oncologist.* 2011;16:896-903.
12. Balamurugan A, Rees JR, Kosary C, Rim SH, Li J, Stewart S. Subsequent primary cancers among men and women with in situ and invasive melanoma of the skin. *J Am Acad Dermatol.* 2011;65(5 suppl 1):S69-S77.
13. Francken AB, Shaw HM, Thompson JF. Detection of second primary cutaneous melanomas. *Eur J Surg Oncol.* 2008;34: 587-592.
14. Wassberg C, Thorn M, Yuen J, Hakulinen T, Ringborg U. Cancer risk in patients with earlier diagnosis of cutaneous melanoma in situ. *Int J Cancer.* 1999;83:314-317.
15. McCaul KA, Fritschl L, Baade P, Coory M. The incidence of second primary invasive melanoma in Queensland, 1982-2003. *Cancer Causes Control.* 2008;19:451-458.
16. Thorn M, Ponten F, Johansson AM, Bergstrom R. Rapid increase in diagnosis of cutaneous melanoma in situ in Sweden, 1968-1992. *Cancer Detect Prev.* 1998;22:430-437.
17. Purdue MP, Freeman LE, Anderson WF, Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. *J Invest Dermatol.* 2008;128: 2905-2908.
18. Lasithiotakis K, Leiter U, Meier F, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer.* 2008;112: 1795-1804.
19. Buettner PG, Leiter U, Eigentler TK, Garbe C. Development of prognostic factors and survival in cutaneous melanoma over 25 years: an analysis of the Central Malignant Melanoma Registry of the German Dermatological Society. *Cancer.* 2005; 103:616-624.
20. Coory M, Baade P, Aitken J, Smithers M, McLeod GR, Ring I. Trends for in situ and invasive melanoma in Queensland, Australia, 1982-2002. *Cancer Causes Control.* 2006;17:21-27.
21. Aitken JF, Janda M, Elwood M, Youl PH, Ring IT, Lowe JB. Clinical outcomes from skin screening clinics within a community-based melanoma screening program. *J Am Acad Dermatol.* 2006;54:105-114.
22. Bradford PT, Freedman DM, Goldstein AM, Tucker MA. Increased risk of second primary cancers after a diagnosis of melanoma. *Arch Dermatol.* 2010;146:265-272.
23. Chen ST, Geller AC, Tsao H. Update on the epidemiology of melanoma. *Curr Dermatol Rep.* 2013;2:24-34.
24. Frangos JE, Duncan LM, Piris A, et al. Increased diagnosis of thin superficial spreading melanomas: a 20-year study. *J Am Acad Dermatol.* 2012;67:387-394.
25. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality; 2009.
26. Wolff T, Tai E, Miller T. Screening for skin cancer: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2009;150:194-198.
27. Waldmann A, Nolte S, Weinstock MA, et al. Skin cancer screening participation and impact on melanoma incidence in Germany—an observational study on incidence trends in regions with and without population-based screening. *Br J Cancer.* 2012;106:970-974.
28. Breitbart EW, Waldmann A, Nolte S, et al. Systematic skin cancer screening in Northern Germany. *J Am Acad Dermatol.* 2012;66:201-211.
29. Eisemann N, Waldmann A, Geller AC, et al. Non-melanoma skin cancer incidence and impact of skin cancer screening on incidence. *J Invest Dermatol.* 2014;134: 43-50.
30. Waldmann A, Nolte S, Geller AC, et al. Frequency of excisions and yields of malignant skin tumors in a population-based screening intervention of 360,288 whole-body examinations. *Arch Dermatol.* 2012;148:903-910.
31. Burton RC, Howe C, Adamson L, et al. General practitioner screening for melanoma: sensitivity, specificity, and effect of training. *J Med Screen.* 1998;5:156-161.
32. Jonna BP, Delfino RJ, Newman WG, Tope WD. Positive predictive value for presumptive diagnoses of skin cancer and compliance with follow-up among patients attending a community screening program. *Prev Med.* 1998;27: 611-616.
33. Fritschl L, Dye SA, Katris P. Validity of melanoma diagnosis in a community-based screening program. *Am J Epidemiol.* 2006;164:385-390.
34. de Rooij MJ, Rampen FH, Schouten LJ, Neumann HA. Volunteer melanoma screenings. Follow-up, compliance, and outcome. *Dermatol Surg.* 1997;23:197-201.
35. de Rooij MJ, Rampen FH, Schouten LJ, Neumann HA. Skin cancer screening focusing on melanoma yields more selective attendance. *Arch Dermatol.* 1995;131:422-425.
36. Engelberg D, Gallagher RP, Rivers JK. Follow-up and evaluation of skin cancer screening in British Columbia. *J Am Acad Dermatol.* 1999;41:37-42.
37. Geller AC, Zhang Z, Sober AJ, et al. The first 15 years of the American Academy of Dermatology skin cancer screening programs: 1985-1999. *J Am Acad Dermatol.* 2003;48:34-41.
38. Geller AC, Sober AJ, Zhang Z, et al. Strategies for improving melanoma education and screening for men age >or= 50 years: findings from the American Academy of Dermatological National Skin Cancer Screening Program. *Cancer.* 2002;95:1554-1561.
39. Koh HK, Norton LA, Geller AC, et al. Evaluation of the American Academy of Dermatology's National Skin Cancer Early Detection and Screening Program. *J Am Acad Dermatol.* 1996;34:971-978.
40. Gelfand J. Behind the numbers: number needed to screen. *NEJM Journal Watch.* December 22, 2011. Available at: <http://www.targetportraits.com/products/images-cd>. Accessed May 11, 2015.
41. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet.* 1999;354: 723-729.

42. Stanton WR, Janda M, Baade PD, Anderson P. Primary prevention of skin cancer: a review of sun protection in Australia and internationally. *Health Promot Int.* 2004;19:369-378.
43. Weiss J, Kirsner RS, Hu S. Trends in primary skin cancer prevention among US Hispanics: a systematic review. *J Drugs Dermatol.* 2012;11:580-586.
44. Buller DB, Cokkinides V, Hall HI, et al. Prevalence of sunburn, sun protection, and indoor tanning behaviors among Americans: review from national surveys and case studies of 3 states. *J Am Acad Dermatol.* 2011;65(5 suppl 1):S114-S123.
45. Petersen B, Wulf HC. Application of sunscreen—theory and reality. *Photodermat Photoimmunol Photomed.* 2014;30:96-101.
46. Ou-Yang H, Stanfield J, Cole C, Appa Y, Rigel D. High-SPF sunscreens ($\text{SPF} \geq 70$) may provide ultraviolet protection above minimal recommended levels by adequately compensating for lower sunscreen user application amounts. *J Am Acad Dermatol.* 2012;67:1220-1227.
47. Teramura T, Mizuno M, Asano H, Naito N, Arakane K, Miyachi Y. Relationship between sun-protection factor and application thickness in high-performance sunscreen: double application of sunscreen is recommended. *Clin Exp Dermatol.* 2012;37:904-908.
48. Lee TK, Rivers JK, Gallagher RP. Site-specific protective effect of broad-spectrum sunscreen on nevus development among white schoolchildren in a randomized trial. *J Am Acad Dermatol.* 2005;52:786-792.
49. Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. *JAMA.* 2000;283:2955-2960.
50. Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med.* 2003;139:966-978.
51. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am J Public Health.* 2002;92:1173-1177.
52. Lazovich D, Vogel RI, Berwick M, Weinstock MA, Warshaw EM, Anderson KE. Melanoma risk in relation to use of sunscreen or other sun protection methods. *Cancer Epidemiol Biomarkers Prev.* 2011;20:2583-2593.
53. Autier P, Dore JF, Cattaruzza MS, et al. Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. *J Natl Cancer Inst.* 1998;90:1873-1880.
54. Autier P. Sunscreen abuse for intentional sun exposure. *Br J Dermatol.* 2009;161(suppl 3):40-45.
55. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol.* 2011;29:257-263.
56. Pissavini M, Diffey B. The likelihood of sunburn in sunscreen users is disproportionate to the SPF. *Photodermat Photoimmunol Photomed.* 2013;29:111-115.
57. Liu W, Wang X, Lai W, et al. Sunburn protection as a function of sunscreen application thickness differs between high and low SPFs. *Photodermat Photoimmunol Photomed.* 2012;28:120-126.
58. Gordon LG, Scuffham PA, van der Pols JC, McBride P, Williams GM, Green AC. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. *J Invest Dermatol.* 2009;129:2766-2771.
59. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2546-2548.
60. Thompson SC, Jolley D, Marks I. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med.* 1993;329:1147-1151.
61. Dupuy A, Dunant A, Grob JJ. Randomized controlled trial testing the impact of high-protection sunscreens on sun-exposure behavior. *Arch Dermatol.* 2005;141:950-956.
62. Idorn LW, Datta P, Heydenreich J, Philipsen PA, Wulf HC. A 3-year follow-up of sun behavior in patients with cutaneous malignant melanoma. *JAMA Dermatol.* 2014;150:163-168.
63. Bartoli C, Bono A, Clemente C, Del Prato ID, Zurrida S, Cascinelli N. Clinical diagnosis and therapy of cutaneous melanoma in situ. *Cancer.* 1996;77:888-892.
64. Andre J, Moulonguet I, Goettmann-Bonvallot S. In situ amelanotic melanoma of the nail unit mimicking lichen planus: report of 3 cases. *Arch Dermatol.* 2010;146:418-421.
65. Cliff S, Otter M, Holden CA. Amelanotic lentigo maligna melanoma of the face: a case report and review of the literature. *Clin Exp Dermatol.* 1997;22:177-179.
66. Pichler E, Fritsch P. Macular amelanotic melanoma in situ. *Dermatologica.* 1988;177:313-316.
67. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. *Br J Dermatol.* 1987;116:303-310.
68. Tannous ZS, Lerner LH, Duncan LM, Mihm MC Jr, Flotte TJ. Progression to invasive melanoma from malignant melanoma in situ, lentigo maligna type. *Hum Pathol.* 2000;31:705-708.
69. Cohen LM. Lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol.* 1997;36:913.
70. Dubow BE, Ackerman AB. Ideas in pathology. Malignant melanoma in situ: the evolution of a concept. *Mod Pathol.* 1990;3:734-744.
71. Flotte TJ, Mihm MC Jr. Lentigo maligna and malignant melanoma in situ, lentigo maligna type. *Hum Pathol.* 1999;30:533-536.
72. World Health Organization Classification of Tumours. In: LeBoit PE, Burg G, Weedon D, Sarasain A, eds. *Pathology and Genetics of Skin Tumours.* 2006. Lyon, France: IARC Press.
73. Seidenari S, Ferrari C, Borsari S, et al. The dermoscopic variability of pigment network in melanoma in situ. *Melanoma Res.* 2012;22:151-157.
74. Burroni M, Sbano P, Cevenini G, et al. Dysplastic naevus vs. in situ melanoma: digital dermoscopy analysis. *Br J Dermatol.* 2005;152:679-684.
75. Seidenari S, Ferrari C, Borsari S, et al. Reticular grey-blue areas of regression as a dermoscopic marker of melanoma in situ. *Br J Dermatol.* 2010;163:302-309.
76. Silva VP, Ikino JK, Sens MM, Nunes DH, Di Giunta G. Dermoscopic features of thin melanomas: a comparative study of melanoma in situ and invasive melanomas smaller than or equal to 1mm. *An Bras Dermatol.* 2013;88:712-717.
77. Seidenari S, Bassoli S, Borsari S, et al. Variegated dermoscopy of in situ melanoma. *Dermatology.* 2012;224:262-270.
78. Borsari S, Longo C, Ferrari C, et al. Dermoscopic island: a new descriptor for thin melanoma. *Arch Dermatol.* 2010;146:1257-1262.

79. Mahlberg MJ, Hwa C, Kopf AW, Stein JA. Letter: "mushroom-cloud sign" of melanoma. *Dermatol Surg.* 2011;37:1546-1548.
80. Kaminska-Winciorek G, Właszcuk P, Wydmanski J. "Mistletoe sign": probably a new dermoscopic descriptor for melanoma *in situ* and melanocytic junctional nevus in the inflammatory stage. *Postepy Dermatol Alergol.* 2013;30:316-319.
81. Stante M, Giorgi V, Stanganelli I, Alfaioli B, Carli P. Dermoscopy for early detection of facial lentigo maligna. *Br J Dermatol.* 2005;152:361-364.
82. Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. *J Am Acad Dermatol.* 2003;48:679-693.

Melanoma in situ

Part II. Histopathology, treatment, and clinical management

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Learning objectives

Describe appropriate treatment margins and modalities for MIS and discuss appropriate recommendations for genetic testing for patients with MIS and their family members.

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Melanoma in situ (MIS) poses special challenges with regard to histopathology, treatment, and clinical management. The negligible mortality and normal life expectancy associated with patients with MIS should guide treatment for this tumor. Similarly, the approach to treatment should take into account the potential for MIS to transform into invasive melanoma, which has a significant impact on morbidity and mortality. Part II of this continuing medical education article reviews the histologic features, treatment, and management of MIS. (J Am Acad Dermatol 2015;73:193-203.)

Key words: lentigo maligna; melanoma; melanoma in situ.

HISTOPATHOLOGY OF MELANOMA IN SITU

Key points

- The histopathologic diagnosis of melanoma in situ can be difficult
- Immunohistochemical stains may aid in the diagnosis by highlighting junctional melanocytes
- Microphthalmia transcription factor (MITF) and SOX10 are emerging as the preferred

immunohistochemical stains to aid in the diagnosis of melanoma in situ

- Atypical melanocytic hyperplasia in the setting of sun-damaged skin represents an important diagnostic challenge and can be difficult to differentiate from early melanoma in situ, particularly lentigo maligna

Melanoma in situ (MIS) is a proliferation of malignant melanocytes within the epidermis without

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Abbreviations used:

IHC:	immunohistochemical
MIS:	melanoma in situ
LM:	lentigo maligna
MM:	malignant melanoma
MMS:	Mohs micrographic surgery
SEER:	Surveillance, Epidemiology, and End Results
WLE:	wide local excision

invasion into the dermis. The criteria for histologic diagnosis include: (1) poor circumscription; (2) asymmetry; (3) a predominance of individual melanocytes over nests with (a) confluent growth along the dermoepidermal junction, (b) effacement of rete ridges, and (c) pagetoid scatter; (4) nests of atypical melanocytes with (a) confluence, (b) variability in shape and size, and (c) consumption of epidermis; (5) haphazard distribution; and (6) involvement of adnexal epithelium. The morphology of MIS may differ according to the histologic variant, which includes lentigo maligna (LM), superficial spreading, acral lentiginous, and mucosal. LM has effacement of the rete ridges and a proliferation of atypical melanocytes primarily along the basal layer with single cells predominating over nests of cells and variable pagetoid spread. Superficial spreading MIS is remarkable for pagetoid spread with single cells and groups of atypical melanocytes scattered throughout the epidermis into the granular or horny layers. Acral lentiginous MIS features a hyperplastic epidermis with lentiginous proliferation of atypical melanocytes, sometimes with prominent dendrites, that has variable density, atypia, and pagetoid scatter. Mucosal MIS shares histologic features of both acral lentiginous melanoma and LM.

Occasional overlapping features between all variants of MIS may be seen, and involvement of the adnexal epithelium is a common feature.¹

It can be challenging to accurately assess the number of junctional melanocytes present on microscopic evaluation of MIS. In such cases, immunohistochemical (IHC) stains may be used to help differentiate melanocytes from surrounding keratinocytes. A number of commercially available melanocytic markers exist, but their use depends on the preference or experience of the dermatopathologist. Some of the emerging preferred stains for MIS include microphthalmia transcription factor (MITF) and SOX10, which highlight the nuclei of melanocytes, thereby avoiding confusion with staining of pigmented keratinocytes that may be seen with markers of melanosome epitopes, such as Melan-A/MART-1.^{2,3} Fig 1 shows an example of MIS

stained with hematoxylin–eosin (Fig 1, A) and MITF (Fig 1, B). The technical quality of IHC stains is often laboratory-dependent, and it is of paramount importance that the dermatopathologist is familiar with the given laboratory's staining patterns and pitfalls.

Another obstacle in the histologic diagnosis of MIS is the recognition of pseudomelanocytic nests at the dermoepidermal junction, which may be seen in the setting of lichenoid inflammation. Pseudomelanocytic nests resemble melanocytic nests, but they label with melanocytic markers and with keratinocytic, macrophage, and T cell markers.⁴ Fig 1 shows pseudonests of lichenoid dermatitis stained with hematoxylin–eosin (Fig 1, C) and MITF (Fig 1, D). This pitfall highlights the importance of careful interpretation of IHC stains and close clinical pathologic correlation.

In patients with LM (MIS on sun-damaged skin), atypical junctional melanocytic proliferations and melanocytic hyperplasia represent an important diagnostic challenge because they can be extremely difficult to differentiate from early MIS. These lesions consist of poorly defined proliferations of junctional melanocytes, which lack the prominent cellular atypia or density to meet the criteria of a fully developed MIS. In addition, the distinct criteria for MIS may not be present in all portions of any given MIS lesion. Some studies have attempted to define the expected background density of melanocytes in sun-damaged skin; the results suggest that chronically sun-exposed skin demonstrates increased melanocytic density.⁵ However, it is clear that there is a high degree of variability in melanocytic density.⁶ Some attempts have been made to define criteria that would help differentiate MIS from melanocytic hyperplasia of sun-damaged skin. Criteria that support a diagnosis of MIS over melanocytic hyperplasia of sun-damaged skin include the presence of melanocytic nests, an irregular distribution of melanocytes, the descent of melanocytes along the adnexal structures, the presence of melanocytes above the dermoepidermal junction, an increased number of melanocytes, pleomorphism and atypia of melanocytes, and an irregular distribution of pigment.^{6,7} However, these criteria are not fully reliable.^{6,7}

In everyday practice, these cases are difficult and challenging because of concern about the under- or overdiagnosis of MIS. The ambiguous histopathology based on obtained biopsy specimens often mandates complete excision to establish a more definitive final diagnosis.

There is occasional disagreement between experts in the diagnosis of melanocytic lesions;

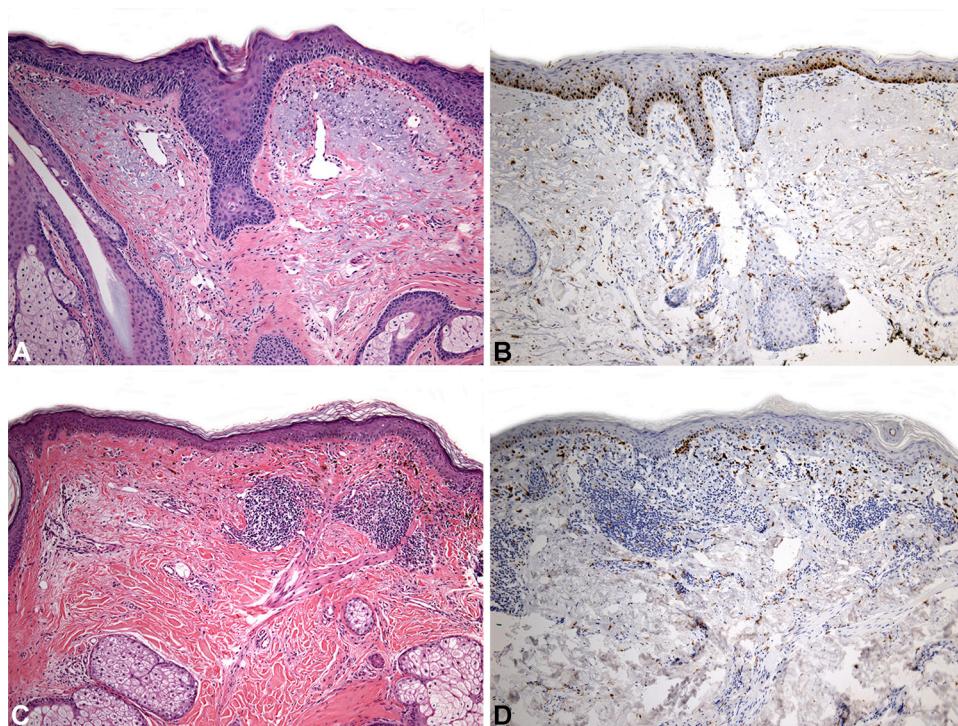


Fig 1. **A**, Hematoxylin–eosin staining of melanoma in situ. **B**, Microphthalmia transcription factor immunostaining of melanoma in situ. **C**, Hematoxylin–eosin staining of pseudonests of lichenoid dermatitis. **D**, Microphthalmia transcription factor immunostaining of lichenoid dermatitis. (*A-D*, original magnification: $\times 10$.)

however, expert review of problematic cases can improve patient care. It is imperative to recognize that partial biopsy specimens of melanocytic lesions are problematic and may be inadequate for accurate diagnosis (Table I).⁸ In addition, partial biopsy specimens of MIS may be misinterpreted as benign. It is well recognized that margins of MIS are difficult to evaluate on frozen sections and are not considered the best choice for the accurate assessment of surgical margins.⁹

CURRENT RECOMMENDATIONS AND TRENDS IN THE TREATMENT OF MELANOMA IN SITU

Key points

- **Excisional margins of 0.5 cm are considered the standard treatment for melanoma in situ, but the lack of randomized controlled trials supporting this standard is noteworthy**
- **There is evidence to support wider margins (ranging between 0.5-1.0 cm)**

Because of the potential of MIS to transform into malignant melanoma (MM) and the possibility of sampling error in biopsy specimens of larger melanocytic lesions, excision with at least 0.5-cm margins is recommended.¹⁰⁻¹² Based on

Table I. Studies examining melanoma in situ tumors with invasive component found on surgical removal

Study	No. of MIS lesions	No. of MIS lesions found to have invasive component (% of total MIS lesions)
Megahed et al ²¹	104	30 (29)
Zalla et al ²²	46	3 (7)
Somach et al ²³	46	9 (20)
Weodon et al ²⁴	66	8 (12)
Bub et al ³⁶	58	3 (5)
Cohen et al ¹¹²	29	3 (10)
Bosbous et al ⁴⁰	59	6 (10)

Surveillance, Epidemiology, and End Results (SEER) data, treatment of MIS has evolved over time, with the proportion of tumors excised with <1-cm margins increasing over the past 3 decades (Table II). This trend likely reflects consensus guidelines, released in the 1990s, suggesting 0.5-cm margins as the optimal surgical excisional margins for MIS.¹³⁻¹⁶ Different surgical excisional margins (<1 cm vs ≥ 1 cm) did not influence MIS-related survival.¹⁷ Investigations into appropriate margins for the treatment of MIS are ongoing, and will likely continue to be a topic of discussion in the coming years.

Table II. Excisional margins of melanoma in situ, based on Surveillance, Epidemiology, and End Results data, 1973-2006

Margins	1973-1985	1986-1995	1996-2006
Excisional biopsy not otherwise specified	1795 (58%)	1472 (10%)	3718 (5%)
Excisional margins <1 cm	835 (27%)	7634 (53%)	43,435 (57%)
Excisional margins ≥1 cm	485 (15%)	5343 (37%)	29,136 (38%)

Data from National Institutes of Health Consensus Development Conference Statement on Diagnosis and Treatment of Early Melanoma, 1973-2006.¹⁶

Current margin recommendations are largely based on clinical dogma and consensus discussion, and therefore warrant more rigorous evaluation. Guidelines in Australia and New Zealand rate the 0.5-cm excision margin recommendation as grade C, in which the “body of evidence provides some support for recommendations but care should be taken in its application.”¹⁸ Likewise, the American Academy of Dermatology also graded the 0.5-cm margin for MIS as “III,” representing the lowest rank on the grading scale. Level III indicates that the recommendation was made based on “other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence.”¹⁹ The American Academy of Dermatology guidelines recommend excisional margins between 0.5 and 1.0 cm, based on clinical judgment.¹⁹ The lack of randomized controlled trials supporting the 0.5-cm margin for MIS is striking, especially since 0.5-cm excisional margins are often considered the standard approach to treatment.

The varying literature on MIS excision margins can create confusion for dermatologists. In a 2005 survey of 597 dermatologists, 55% responded that they would take ≤5-mm margins for a nonfacial MIS, and 33% responded that they would take >5-mm margins. For a facial MIS, 57% responded that they would take ≤5-mm margins, while 24% responded that they would take >5-mm margins. In this same survey, 10% of dermatologists considered MIS a premalignant/precancerous growth; 84% considered it a malignancy/cancer.²⁰

UPSTAGING TO MALIGNANT MELANOMA

Key points

- Based on the literature, a range of 5% to 29% of melanoma in situ cases are upstaged to invasive malignant melanoma after review of the pathology specimen obtained from complete excision

- Upstaging occurs more frequently after shave biopsy specimens

In a review of the literature, approximately 5% to 29% of MIS lesions actually proved to have at least 1 focus of invasion upon surgical excision. This finding upstaged the initial diagnosis of MIS to MM, but varied widely because of study sample sizes, which ranges from 66 to 104 patients. When combining data from all of the studies, approximately 19% of MIS lesions were upstaged to MM (Table II).^{8,21-24} This may be due to inadequate sampling within a mottled lesion with multiple morphologies resulting in a nonrepresentative biopsy specimen. Upstaging after biopsy occurs most frequently after shave biopsies compared to punch or excisional biopsies. In a review of 609 patients, 59 (10%) of patients were upstaged after surgical excision. Of these cases, 64% had been obtained by shave biopsy, compared to 27% obtained by punch biopsy.²⁵ Therefore, it is prudent for physicians to obtain multiple scouting biopsy specimens in a lesion with multiple morphologies or in a large lesion with concern of focal invasion. Biopsy specimens should always include a portion of the lesion with the most concerning morphology.

TREATMENT: SURGICAL REMOVAL

Key points

- Surgical removal may be performed by wide local excision, staged excision with expedited permanent sections, or Mohs micrographic surgery
- Margins of 0.5 to 0.6 cm result in varying clearance rates and wider margins may be necessary for tumor removal

Various surgical options can be used for the treatment of MIS. These include wide local excision (WLE), staged excision, and Mohs micrographic surgery (MMS). WLE aims to remove the clinically apparent tumor and a surrounding margin of normal tissue. Staged excision removes the clinically apparent lesion and uses rushed permanent sections to identify the excised tissue for margin control. If margins are positive, additional tissue is surgically removed. Final closure of the wound bed is delayed until permanent sections show clear margins. MMS uses frozen sections to examine all portions of the epidermis. This technique can be combined with IHC stains to better delineate surgical margins.

Because of unpredictable subclinical extension commonly associated with MIS, particularly on sun-damaged skin or for LM, WLE with 0.5-cm margins may be inadequate for tumor extirpation. Table III shows the margins needed for clearance of

Table III. Surgical margins required for clearance of melanoma in situ

Study	Sample size	Surgical removal	Sectioning	Margin size (cm)	Clearance rates (%)
Agarwal-Antal et al ³⁸	92	MMS	Permanent	0.5	42
Bienert et al ²⁷	97	MMS	Frozen and permanent	0.5	0
Albertini et al ²⁶	42	MMS	Frozen	0.5	24
				0.6	41
Zalla et al ²²	46	MMS	Frozen	≤0.6	50
				≤1	83
				≤1.2	91
				≤1.5	96
				≤1.9	98
Bricca et al ²⁸	331	MMS	Frozen	0.6	89
				0.9	98.5
				1.2	98.8
				2.4	100
Kunishige et al ²⁹	1120	MMS	Frozen	0.6	86
				0.9	98.9
				1.2	99.4
				1.5	99.6
				3	100

Data from Kunishige et al.²⁹

MMS, Mohs micrographic surgery.

MIS in various studies. Margin clearance rates with 0.5- to 0.6-cm margins range from 0% to 89%.^{22,26-29} Therefore, the currently accepted 0.5-cm margins for the treatment of MIS, recommended based on a consensus conference, may be inadequate.^{30,31}

The size and type of the initial tumor should also be taken into consideration when determining excisional margins. LMs often have subclinical margins, and are more likely to be incompletely excised compared to non-LM MIS.³² Robinson et al³³ found that larger LMs often required a wide margin for excision, with tumors >3 cm requiring a margin of ≤1 cm for resection. In contrast, tumors <2 cm required margins <1 cm.

STAGED EXCISION

Key points

- Staged excision is a means of improving margin control through sequential surgical removal of tissue after examination of the edges by pathology using permanent sections
- Methods of staged excision include the square technique and the spaghetti technique

Occasionally, because of the finding of positive margins after initial excision, additional tissue needs to be removed. Staged surgical excision with permanent section avoids the limitations of removal by MMS, which is an approach that has not yet been standardized. Several approaches and techniques

have been reported for staged excision of MIS. Johnson et al³⁴ developed a square technique for LM in which the tumor is first illuminated with a Wood's lamp. Next, a double-lined square is outlined with a 0.5- to 1-cm margin from the tumor. Afterward, the outer perimeter of the square is excised and closed. Positive margins are marked on a map, and the patient returns for reexcision of these areas. When all margins are clear, the central bulk of the tumor is excised as the last step.³⁴ The spaghetti technique is similar to the square technique, except that outlines are drawn to match the clinical contour of the lesion, instead of in a square. The central tumor is also excised as the last step.³⁵ Several other staged surgical excision techniques have been described, with varying geographic shapes and contours used to excise the tumor.^{34,36-46}

MOHS MICROGRAPHIC SURGERY

Key points

- Mohs surgery for melanoma in situ has shown variable clearance rates and success
- Because of the difficulty of accurately visualizing melanocytes on frozen sections, its success is dependent on the skill of the technician and surgeon
- Immunohistochemical stains have been employed to better delineate melanocytes on frozen sections

In order to preserve tissue in locations where MIS frequently occurs, some have proposed using the

Table IV. Studies examining recurrence rates of melanoma in situ treated with Mohs micrographic surgery

Study	No. of MIS lesions	Surgery type	Follow-up time (months)	Recurrence rate (%)
Zitelli et al ¹¹⁶	184	MMS	50	0.5
Bienert et al ²⁷	76	MMS	33	0
Bricca et al ²⁸	331	MMS, HMG-45 in 33% of lesions	58	0.3
Bene et al ¹¹⁷	116	MMS, frozen and permanent sections	63	1.8
Cohen et al ¹¹²	26	MMS	58	2.2
Clayton et al ¹¹⁵	77	MMS	22	1
Agarwal-Antal et al ³⁸	92	MMS	48	0
Hill et al ¹¹⁸	38	Staged excision	25	2.6
Huilgol et al ¹¹³	125	Staged excision	38	2
Bub et al ³⁶	55	Staged excision	57	3.6
Moller et al ⁴⁴	49	Staged excision	14	0
Walling et al ⁴⁶	50	Staged excision	96	7
Johnson et al ³⁴	35	Staged excision	0	0
Malhotra et al ¹¹⁹	109	Staged excision	32	3.7
Mahoney et al ¹²⁰	11	Staged excision	4.7	0
Jejurikar et al ¹²¹	42	Staged excision	31	0
Bosbous et al ⁴⁰	49	Staged excision	26	1.7
Lee et al ¹²²	31	Staged excision	42	10

Data from McLeod et al.¹¹⁴

FS, Frozen section; HMG, human melanoma black; PS, permanent section.

Mohs microscopically controlled surgery approach. In this method, surgeons examine frozen sections of tissue cut to allow for visualization of 100% of the epidermis. Frozen sections are often not suitable for the accurate diagnosis of melanocytic lesions.⁹ Therefore, IHC stains, such as HMB-45, MEL-5, MITF, and MART-1, are often used to better delineate melanocytes on frozen sections.⁴⁷⁻⁵¹ Several studies have examined recurrence rates of MIS after treatment with MMS, varying from 0% to 10% (Table IV). The use of MMS is limited by several factors, including the experience of the treating surgeon, the skill of the laboratory technician in cutting and staining the tissue for frozen sections, and avoiding freeze artifact.⁵² In frozen sections, melanocytes lack the shrinkage artifact often seen in permanent sections, and instead appear plump with prominent cytoplasm that can be easily mistaken for keratinocytes.^{47,50} Because the MMS approach to treating MIS has not been standardized and depends to a large degree on the skill of the surgeon and histopathology technician, evaluating the outcomes from different centers is difficult.⁵²⁻⁵⁴

TOPICAL THERAPY

Imiquimod

Key points

- **Imiquimod is not FDA approved for the treatment of melanoma in situ; its use is therefore considered off-label**
- **Clearance rates with imiquimod can vary widely**

There are several case reports and open-label studies of the use of imiquimod 5% cream for treatment of MIS, LM subtype.⁵⁵ Imiquimod is an immune response modifier that works by activating Toll-like receptor 7 (TLR-7) and causes a localized immune response at the targeted site(s). It is approved by the US Food and Drug Administration for the treatment of superficial basal cell carcinoma, actinic keratosis, and genital warts. Its use for MIS is considered off-label but has been described in the literature.⁵⁶

Clearance rates with imiquimod vary widely, with some MIS lesions failing to respond at all and others clearing 100% with no evidence of recurrence.⁵⁷⁻⁶⁹ Treatment regimens also varied widely, with some using the medication several days a week and others using it only once weekly. Similarly, the treatment period ranged from 4 to 36 weeks. In some cases, tumor recurred as LM melanoma, highlighting the risk that imiquimod may not treat deeper components of the tumor.^{66,70} A rigorous protocol using daily applications of imiquimod for 12 weeks has been proposed for the treatment of MIS. There must be clinical erythema during a minimum of 10 of the 12 weeks.⁷¹ Of note, residual clinical hyperpigmentation can still be present in lesions treated with imiquimod, even with histologic clearance of MIS.^{63,71-73}

In addition to the use of imiquimod as monotherapy, this medication can also be used in conjunction with tazarotene and surgical excision.^{59,74-76} In 1 study of 40 patients, use of

imiquimod 5 times a week for 3 months before staged excision resulted in no recurrences at 18 months.⁷⁵ Patients who use imiquimod plus tazarotene may have even better responses compared to the use of imiquimod alone.⁵⁹ However, there is a lack of randomized controlled trials examining the use of imiquimod with or without tazarotene before surgery compared with surgery alone. Therefore, definitive conclusions cannot be drawn. The well-known adverse effects of pruritus, erythema, irritation, and flu-like systemic symptoms, though tolerable, also need to be considered when choosing imiquimod for the treatment of MIS.⁷⁷⁻⁷⁹

While the use of imiquimod 5% cream has been examined in several case series of LM on facial locations, its use in non-LM MIS is infrequently reported. Three case reports were found in a review of the literature. In 2 of the cases, the tumor was recurrent after several treatments, including MMS, at which point imiquimod 5% cream was used.^{66,80} In 1 case, the tumor developed an invasive component during the course of imiquimod treatment.⁶⁶ Use of imiquimod for primary treatment of MIS, non-LM types is poorly studied and therefore is not advisable as off-label monotherapy.

Intralesional interferon-alfa

Key point

- **Intralesional interferon-alfa has been successfully used for the treatment of melanoma in situ in several case reports**

Several reports have examined the use of interferon-alfa (IFN- α) for the treatment of MIS. Carucci and Leffell⁸¹ successfully treated recurrent MIS of the upper and lower eyelid with 3 million units of intralesional IFN- α 3 times per week (39 million units total). Posttreatment biopsy specimens revealed clearance of the tumor.⁸¹ Cornejo et al⁸² achieved biopsy-proven clearance in 9 of 11 cases treated with IFN- α . Their treatment regimen included 3 million units for tumors ≤ 2.5 cm and 6 million units for tumors > 2.5 cm, 3 times per week. The mean treatment duration was 15.4 months (range, 4-40 months).⁸² Turner et al⁸³ reported a woman with xeroderma pigmentosa and 10 MIS lesions. Tumors were treated with either 1 million units of IFN- α or placebo and surgically excised for histologic examination. MIS treated with IFN- α showed no evidence of residual MIS, whereas those treated with placebo showed the presence of a tumor.⁸³

Other topical medications

Key point

- **There are case reports regarding the use of other topical medications for the treatment of melanoma in situ**

5-Flourouracil,⁸⁴⁻⁸⁶ azelaic acid,⁸⁷⁻⁹⁴ and retinoic acid derivatives^{59,95,96} have also been investigated as treatments for MIS. These are mostly small case series or case reports and should not be considered first-line treatments for MIS.

RADIATION

Key point

- **There are limited studies on the use of radiation for melanoma in situ**

There are a limited number of studies investigating the use of radiation for MIS. Grenz rays and fractionated radiotherapy have varying degrees of success.^{97,98} Recurrence rates range from 0% to 20%, and side effects include radiation dermatitis, telangiectasias, hypo- or hyperpigmentation, erythema, and the development of other neoplasms, such as basal and squamous cell carcinoma.⁹⁸⁻¹⁰² Radiation therapy is not considered a first-line treatment but may be appropriate depending on other factors, such as lesion size, anatomic site, and patient comorbidity.

LASER THERAPY

Key point

- **Recurrence after laser therapy can be as high as 38%**

Several lasers have been used to treat MIS in case reports and case series. These lasers include CO₂, Q-switched neodymium-doped yttrium aluminium garnet, Q-switched ruby, argon, and alexandrite. Combinations of these laser modalities have also been tried. The largest case series involved 22 patients treated with the Q-switched neodymium-doped yttrium aluminium garnet laser. Recurrence rates were 23% after a follow-up of <3 months.¹⁰³ When evaluated as a class of treatment, recurrence rates of MIS treated with laser were as high as 38%, with some progressing to LM melanoma.¹⁰³⁻¹¹¹ A major challenge with laser therapy is the absence of histopathology to evaluate the presence of invasive components and confirmation of complete extirpation of the tumor.

In conclusion, our understanding of melanoma in situ and its treatment is evolving. The histopathologic diagnosis of MIS continues to be challenging, even to expert dermatopathologists. Pseudomelanocytic nests, lichenoid inflammation, and a background of

sun-damaged skin also add to the diagnostic challenge. In addition, obtaining an incomplete biopsy specimen can lead to sampling error, which may result in upstaging to invasive melanoma.

The treatment paradigm for MIS continues to improve with time. Surgical excision remains the standard of care for the treatment of MIS. In addition to wide local excision with at least 0.5-cm margins, staged surgical excision and MMS with frozen section IHC stains may be useful. However, the use of MMS for this purpose requires additional study and is variable depending on the skill of the physician and histotechnician. Second-line treatments—topical agents, intralesional IFN- α , radiation, and laser therapy—may have roles in the primary treatment of patients who are unable to tolerate surgery or as treatment adjuvant to excision. Until the efficacy of these modalities is better proven in the literature, we do not recommend their use as monotherapy.

REFERENCES

1. Tan MAL, Ackerman AB. Criteria for histopathologic diagnosis of melanoma, 1947-2000: a critique in historical perspective. *Dermatopathol Pract Conceptual*. 2001;7:39-53.
2. Buonaccorsi JN, Prieto VG, Torres-Cabala C, Suster S, Plaza JA. Diagnostic utility and comparative immunohistochemical analysis of MITF-1 and SOX10 to distinguish melanoma *in situ* and actinic keratosis: a clinicopathological and immunohistochemical study of 70 cases. *Am J Dermatopathol*. 2014;36:124-130.
3. Kim J, Taube JM, McCalmont TH, Glusac EJ. Quantitative comparison of MiTF, Melan-A, HMB-45 and Mel-5 in solar lentigines and melanoma *in situ*. *J Cutan Pathol*. 2011;38:775-779.
4. Silva CY, Goldberg LJ, Mahalingam M, Bhawan J, Wolpowitz D. Nests with numerous SOX10 and MiTF-positive cells in lichenoid inflammation: pseudo-melanocytic nests or authentic melanocytic proliferation? *J Cutan Pathol*. 2011;38:797-800.
5. Madden K, Forman SB, Elston D. Quantification of melanocytes in sun-damaged skin. *J Am Acad Dermatol*. 2011;64:548-552.
6. Barlow JO, Maize J Sr, Lang PG. The density and distribution of melanocytes adjacent to melanoma and nonmelanoma skin cancers. *Dermatol Surg*. 2007;33:199-207.
7. Weyers W, Bonczkowitz M, Weyers I, Bittinger A, Schill WB. Melanoma *in situ* versus melanocytic hyperplasia in sun-damaged skin. Assessment of the significance of histopathologic criteria for differential diagnosis. *Am J Dermatopathol*. 1996;18:560-566.
8. Scolyer RA, Thompson JF, McCarthy SW, Strutton GM, Elder DE. Incomplete biopsy of melanocytic lesions can impair the accuracy of pathological diagnosis. *Australas J Dermatol*. 2006;47:71-73.
9. Prieto VG, Argenyi ZB, Barnhill RL, et al. Are en face frozen sections accurate for diagnosing margin status in melanocytic lesions? *Am J Clin Pathol*. 2003;120:203-208.
10. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet*. 2005;365:687-701.
11. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med*. 2004;351:998-1012.
12. National Comprehensive Cancer Network. *NCCN guidelines for melanoma*. Fort Washington (PA): National Comprehensive Cancer Network; 2014.
13. Kroon BB, Bergman W, Coebergh JW, Ruiter DJ. Consensus on the management of malignant melanoma of the skin in The Netherlands. Dutch Melanoma Working Party. *Melanoma Res*. 1999;9:207-212.
14. Sober AJ. Diagnosis and management of early melanoma: a consensus view. *Semin Surg Oncol*. 1993;9:194-197.
15. National Institutes of Health Consensus Development Conference Statement on Diagnosis and Treatment of Early Melanoma, January 27-29, 1992. *Am J Dermatopathol*. 1993; 15:34-43.
16. Diagnosis and treatment of early melanoma. NIH Consensus Development Conference. January 27-29, 1992. *Consens Statement / NIH Consensus Development Conference National Institutes of Health Consensus Development Conference*. 1992; 10:1-25.
17. Mocellin S, Nitti D. Cutaneous melanoma *in situ*: translational evidence from a large population-based study. *Oncologist*. 2011;16:896-903.
18. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network Sa.
19. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. *J Am Acad Dermatol*. 2011;65:1032-1047.
20. Charles CA, Yee VS, Dusza SW, et al. Variation in the diagnosis, treatment, and management of melanoma *in situ*: a survey of US dermatologists. *Arch Dermatol*. 2005; 141:723-729.
21. Megahed M, Schon M, Selimovic D, Schon MP. Reliability of diagnosis of melanoma *in situ*. *Lancet*. 2002;359: 1921-1922.
22. Zalla MJ, Lim KK, Dicundo DJ, Gagnot MM. Mohs micrographic excision of melanoma using immunostains. *Dermatol Surg*. 2000;26:771-784.
23. Somach SC, Taira JW, Pitha JV, Everett MA. Pigmented lesions in actinically damaged skin. Histopathologic comparison of biopsy and excisional specimens. *Arch Dermatol*. 1996;132: 1297-1302.
24. Weedon D. A reappraisal of melanoma *in situ*. *J Dermatol Surg Oncol*. 1982;8:774-775.
25. Egnatios GL, Dueck AC, Macdonald JB, et al. The impact of biopsy technique on upstaging, residual disease, and outcome in cutaneous melanoma. *Am J Surg*. 2011;202: 771-777. discussion 7-8.
26. Albertini JG, Elston DM, Libow LF, Smith SB, Farley MF. Mohs micrographic surgery for melanoma: a case series, a comparative study of immunostains, an informative case report, and a unique mapping technique. *Dermatol Surg*. 2002;28:656-665.
27. Bienert TN, Trotter MJ, Arlette JP. Treatment of cutaneous melanoma of the face by Mohs micrographic surgery. *J Cutan Med Surg*. 2003;7:25-30.
28. Bricca GM, Brodland DG, Ren D, Zitelli JA. Cutaneous head and neck melanoma treated with Mohs micrographic surgery. *J Am Acad Dermatol*. 2005;52:92-100.
29. Kunishige JH, Brodland DG, Zitelli JA. Surgical margins for melanoma *in situ*. *J Am Acad Dermatol*. 2012;66: 438-444.
30. NIH Consensus conference. Diagnosis and treatment of early melanoma. *JAMA*. 1992;268:1314-1319.

31. Tzellos T, Kyrgidis A, Mocellin S, Chan A, Pilati P, Apalla Z. Interventions for melanoma in situ, including lentigo maligna. *Cochrane Database Syst Rev.* 2014;12:CD010308.
32. Akhtar S, Bhat W, Magdum A, Stanley PR. Surgical excision margins for melanoma in situ. *J Plast Reconstr Aesthet Surg.* 2014;67:320-323.
33. Robinson JK. Margin control for lentigo maligna. *J Am Acad Dermatol.* 1994;31:79-85.
34. Johnson TM, Headington JT, Baker SR, Lowe L. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure. *J Am Acad Dermatol.* 1997;37:758-764.
35. Gaudy-Marqueste C, Perchenet AS, Tasei AM, et al. The "spaghetti technique": an alternative to Mohs surgery or staged surgery for problematic lentiginous melanoma (lentigo maligna and acral lentiginous melanoma). *J Am Acad Dermatol.* 2011;64:113-118.
36. Bub JL, Berg D, Slee A, Odlund PB. Management of lentigo maligna and lentigo maligna melanoma with staged excision: a 5-year follow-up. *Arch Dermatol.* 2004;140: 552-558.
37. Clark GS, Pappas-Politis EC, Cherpelis BS, et al. Surgical management of melanoma in situ on chronically sun-damaged skin. *Cancer Control.* 2008;15:216-224.
38. Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with permanent sections: implications regarding current guidelines. *J Am Acad Dermatol.* 2002;47:743-748.
39. Abdelmalek M, Loosmore MP, Hurt MA, Hruza G. Geometric staged excision for the treatment of lentigo maligna and lentigo maligna melanoma: a long-term experience with literature review. *Arch Dermatol.* 2012;148: 599-604.
40. Bosbous MW, Dzwierzynski WW, Neuburg M. Staged excision of lentigo maligna and lentigo maligna melanoma: a 10-year experience. *Plast Reconstr Surg.* 2009;124: 1947-1955.
41. Raziano RM, Clark GS, Cherpelis BS, et al. Staged margin control techniques for surgical excision of lentigo maligna. *G Ital Dermatol Venereol.* 2009;144:259-270.
42. Walling HW. Lentigo maligna: current concepts in diagnosis and management. *G Ital Dermatol Venereol.* 2009;144: 149-155.
43. Then SY, Malhotra R, Barlow R, et al. Early cure rates with narrow-margin slow-Mohs surgery for periocular malignant melanoma. *Dermatol Surg.* 2009;35:17-23.
44. Moller MG, Pappas-Politis E, Zager JS, et al. Surgical management of melanoma-in-situ using a staged marginal and central excision technique. *Ann Surg Oncol.* 2009;16: 1526-1536.
45. Hazan C, Dusza SW, Delgado R, Busam KJ, Halpern AC, Nehal KS. Staged excision for lentigo maligna and lentigo maligna melanoma: A retrospective analysis of 117 cases. *J Am Acad Dermatol.* 2008;58:142-148.
46. Walling HW, Scupham RK, Bean AK, Ceiley RI. Staged excision versus Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol.* 2007;57: 659-664.
47. Bricca GM, Brodland DG, Zitelli JA. Immunostaining melanoma frozen sections: the 1-hour protocol. *Dermatol Surg.* 2004;30:403-408.
48. Cherpelis BS, Moore R, Ladd S, Chen R, Glass LF. Comparison of MART-1 frozen sections to permanent sections using a rapid 19-minute protocol. *Dermatol Surg.* 2009;35:207-213.
49. Glass LF, Raziano RM, Clark GS, et al. Rapid frozen section immunostaining of melanocytes by microphthalmia-associated transcription factor. *Am J Dermatopathol.* 2010;32: 319-325.
50. Hendi A, Brodland DG, Zitelli JA. Melanocytes in long-standing sun-exposed skin: quantitative analysis using the MART-1 immunostain. *Arch Dermatol.* 2006;142: 871-876.
51. Kimyai-Asadi A, Ayala GB, Goldberg LH, Vujevich J, Jih MH. The 20-minute rapid MART-1 immunostain for malignant melanoma frozen sections. *Dermatol Surg.* 2008;34:498-500.
52. Zitelli JA, Moy RL, Abell E. The reliability of frozen sections in the evaluation of surgical margins for melanoma. *J Am Acad Dermatol.* 1991;24:102-106.
53. Kimyai-Asadi A, Katz T, Goldberg LH, et al. Margin involvement after the excision of melanoma in situ: the need for complete en face examination of the surgical margins. *Dermatol Surg.* 2007;33:1434-1439. discussion 9-41.
54. Barlow RJ, White CR, Swanson NA. Mohs' micrographic surgery using frozen sections alone may be unsuitable for detecting single atypical melanocytes at the margins of melanoma in situ. *Br J Dermatol.* 2002;146:290-294.
55. Ellis LZ, Cohen JL, High W, Stewart L. Melanoma in situ treated successfully using imiquimod after nonclearance with surgery: review of the literature. *Dermatol Surg.* 2012;38: 937-946.
56. Navi D, Huntley A. Imiquimod 5 percent cream and the treatment of cutaneous malignancy. *Dermatol Online J.* 2004; 10:4.
57. Kallini JR, Jain SK, Khachemoune A. Lentigo maligna: review of salient characteristics and management. *Am J Clin Dermatol.* 2013;14:473-480.
58. Wong JG, Toohe JW, Demers AA, Musto G, Wiseman MC. Topical 5% imiquimod in the treatment of lentigo maligna. *J Cutan Med Surg.* 2012;16:245-249.
59. Hyde MA, Hadley ML, Tristani-Firouzi P, Goldgar D, Bowen GM. A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. *Arch Dermatol.* 2012;148: 592-596.
60. Situm M, Buljan M. Surgical and histologic pitfalls in the management of lentigo maligna melanoma. *G Ital Dermatol Venereol.* 2012;147:21-27.
61. Noel B, Kunzle N. Image in clinical medicine. Lentigo maligna. *N Engl J Med.* 2005;353:2176.
62. Wolf IH, Cerroni L, Kodama K, Kerl H. Treatment of lentigo maligna (melanoma in situ) with the immune response modifier imiquimod. *Arch Dermatol.* 2005;141:510-514.
63. Kamin A, Eigenthaler TK, Radny P, Bauer J, Weide B, Garbe C. Imiquimod in the treatment of extensive recurrent lentigo maligna. *J Am Acad Dermatol.* 2005;52:51-52.
64. Kuper-Bessaguet I, Guillet G, Misery L, Carre JL, Leroy JP, Sassolas B. Topical imiquimod treatment of lentigo maligna: clinical and histologic evaluation. *J American Acad Dermatol.* 2004;51:635-639.
65. Powell AM, Russell-Jones R. Amelanotic lentigo maligna managed with topical imiquimod as immunotherapy. *J Am Acad Dermatol.* 2004;50:792-796.
66. Fisher GH, Lang PG. Treatment of melanoma in situ on sun-damaged skin with topical 5% imiquimod cream complicated by the development of invasive disease. *Arch Dermatol.* 2003;139:945-947.

67. Chapman MS, Spencer SK, Brennick JB. Histologic resolution of melanoma in situ (lentigo maligna) with 5% imiquimod cream. *Arch Dermatol.* 2003;139:943-944.
68. Ahmed I, Berth-Jones J. Imiquimod: a novel treatment for lentigo maligna. *Br J Dermatol.* 2000;143:843-845.
69. Epstein E. Extensive lentigo maligna clearing with topical imiquimod. *Arch Dermatol.* 2003;139:944-945.
70. Woodmansee CS, McCall MW. Recurrence of lentigo maligna and development of invasive melanoma after treatment of lentigo maligna with imiquimod. *Dermatol Surg.* 2009;35:1286-1289.
71. Kirtschig G, van Meurs T, van Doorn R. Twelve-week Treatment of Lentigo Maligna with Imiquimod Results in High and Sustained Clearance Rate. *Acta Derm Venereol.* 2015;95:83-85.
72. Fleming CJ, Bryden AM, Evans A, Dawe RS, Ibbotson SH. A pilot study of treatment of lentigo maligna with 5% imiquimod cream. *Br J Dermatol.* 2004;151:485-488.
73. Powell AM, Russell-Jones R, Barlow RJ. Topical imiquimod immunotherapy in the management of lentigo maligna. *Clin Exp Dermatol.* 2004;29:15-21.
74. Ly L, Kelly JW, O'Keefe R, et al. Efficacy of imiquimod cream, 5%, for lentigo maligna after complete excision: a study of 43 patients. *Arch Dermatol.* 2011;147:1191-1195.
75. Cotter MA, McKenna JK, Bowen GM. Treatment of lentigo maligna with imiquimod before staged excision. *Dermatol Surg.* 2008;34:147-151.
76. Osborne JE, Hutchinson PE. A follow-up study to investigate the efficacy of initial treatment of lentigo maligna with surgical excision. *Br J Plast Surg.* 2002;55:611-615.
77. Cannon PS, O'Donnell B, Huilgol SC, Selva D. The ophthalmic side-effects of imiquimod therapy in the management of periocular skin lesions. *Br J Ophthalmol.* 2011;95:1682-1685.
78. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol.* 2009;145:1431-1438.
79. Murchison AP, Washington CV, Soloman AR, Bernardino CR. Ocular effects of imiquimod with treatment of eyelid melanoma in situ. *Dermatol Surg.* 2007;33:1136-1138.
80. Munoz CM, Sanchez JL, Martin-Garcia RF. Successful treatment of persistent melanoma in situ with 5% imiquimod cream. *Dermatol Surg.* 2004;30:1543-1545.
81. Carucci JA, Leffell DJ. Intralesional interferon alfa for treatment of recurrent lentigo maligna of the eyelid in a patient with primary acquired melanosis. *Arch Dermatol.* 2000;136:1415-1416.
82. Cornejo P, Vanaclocha F, Polimon I, Del Rio R. Intralesional interferon treatment of lentigo maligna. *Arch Dermatol.* 2000;136:428-430.
83. Turner ML, Moshell AN, Corbett DW, et al. Clearing of melanoma in situ with intralesional interferon alfa in a patient with xeroderma pigmentosum. *Arch Dermatol.* 1994;130:1491-1494.
84. Ryan RF, Krementz ET, Litwin MS. A role for topical 5-fluorouracil therapy in melanoma. *J Surg Oncol.* 1988;38:250-256.
85. Coleman WP III, Davis RS, Reed RJ, Krementz ET. Treatment of lentigo maligna and lentigo maligna melanoma. *J Dermatol Surg Oncol.* 1980;6:476-479.
86. Litwin MS, Krementz ET, Mansell PW, Reed RJ. Topical chemotherapy of lentigo maligna with 5-fluorouracil. *Cancer.* 1975;35:721-733.
87. Vereecken P, Heenen M. Recurrent lentigo maligna melanoma: regression associated with local azelaic acid 20%. *Int J Clin Pract.* 2002;56:68-69.
88. Nazzaro-Porro M, Breathnach AS, Balus L, Passi S, Picardo M, Potenza C. A case of recurrent (following surgery x2) invasive malignant melanoma with satellitosis (stage IIIA) successfully resolving after azelaic acid treatment administered by several routes. *Clin Exp Dermatol.* 1996;21:321-323.
89. Rodriguez Prieto MA, Manchado Lopez P, Ruiz Gonzalez I, Suarez D. Treatment of lentigo maligna with azelaic acid. *Int J Dermatol.* 1993;32:363-364.
90. Nazzaro-Porro M, Passi S, Zina G, Breathnach AS. Ten years' experience of treating lentigo maligna with topical azelaic acid. *Acta Derm Venereol Suppl.* 1989;143:49-57.
91. Azelaic acid in lentigo maligna. *Br J Dermatol.* 1987;116:605-607.
92. McLean DI, Peter KK. Apparent progression of lentigo maligna to invasive melanoma during treatment with topical azelaic acid. *Br J Dermatol.* 1986;114:685-689.
93. Leibl H, Stingl G, Pehamberger H, Korschak H, Konrad K, Wolff K. Inhibition of DNA synthesis of melanoma cells by azelaic acid. *J Invest Dermatol.* 1985;85:417-422.
94. Nazzaro-Porro M, Passi S, Balus L, Breathnach A, Martin B, Morpurgo G. Effect of dicarboxylic acids on lentigo maligna. *J Invest Dermatol.* 1979;72:296-305.
95. Chimenti S, Carrozzo AM, Citarella L, De Felice C, Peris K. Treatment of lentigo maligna with tazarotene 0.1% gel. *J Am Acad Dermatol.* 2004;50:101-103.
96. Gaspar ZS, Dawber RP. Treatment of lentigo maligna. *Australas J Dermatol.* 1997;38:1-6; quiz 7-8.
97. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol.* 2002;146:1042-1046.
98. Schmid-Wendtner MH, Brunner B, Konz B, et al. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. *J Am Acad Dermatol.* 2000;43:477-482.
99. Barker CA, Lee NY. Radiation therapy for cutaneous melanoma. *Dermatol Clin.* 2012;30:525-533.
100. Tsang RW, Liu FF, Wells W, Payne DG. Lentigo maligna of the head and neck. Results of treatment by radiotherapy. *Arch Dermatol.* 1994;130:1008-1012.
101. Harwood AR. Conventional fractionated radiotherapy for 51 patients with lentigo maligna and lentigo maligna melanoma. *Int J Radiat Oncol Biol Phys.* 1983;9:1019-1021.
102. Harwood AR. Conventional radiotherapy in the treatment of lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol.* 1982;6:310-316.
103. Madan V, August PJ. Lentigo maligna—outcomes of treatment with Q-switched Nd:YAG and alexandrite lasers. *Dermatol Surg.* 2009;35:607-611. discussion 11-2.
104. Niijima N, Niijima S, Takasu H, Katsuoka K. Progression of lentigo maligna into lentigo maligna melanoma following laser treatment. *Eur J Dermatol: EJD.* 2007;17:252-253.
105. Iyer S, Goldman M. Treatment of lentigo maligna with combination laser therapy: recurrence at 8 months after initial resolution. *J Cosmet Laser Ther.* 2003;5:49-52.
106. Orten SS, Waner M, Dinehart SM, Bardales RH, Flock ST. Q-switched neodymium:yttrium-aluminum-garnet laser treatment of lentigo maligna. *Otolaryngol Head Neck Surg.* 1999;120:296-302.
107. Chan HH, King WW, Chan ES, et al. In vivo trial comparing patients' tolerance of Q-switched Alexandrite (QS Alex) and Q-switched neodymium:yttrium-aluminum-garnet (QS Nd: YAG) lasers in the treatment of nevus of Ota. *Lasers Surg Med.* 1999;24:24-28.

108. Thissen M, Westerhof W. Lentigo maligna treated with ruby laser. *Acta Derm Venereol.* 1997;77:163.
109. Kopera D. Treatment of lentigo maligna with the carbon dioxide laser. *Arch Dermatol.* 1995;131:735-736.
110. Arndt KA. New pigmented macule appearing 4 years after argon laser treatment of lentigo maligna. *J Am Acad Dermatol.* 1986;14:1092.
111. Arndt KA. Argon laser treatment of lentigo maligna. *J Am Acad Dermatol.* 1984;10:953-957.
112. Cohen LM, McCall MW, Zax RH. Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. A follow-up study. *Dermatol Surg.* 1998;24:673-677.
113. Huigol SC, Selva D, Chen C, et al. Surgical margins for lentigo maligna and lentigo maligna melanoma: the technique of mapped serial excision. *Arch Dermatol.* 2004;140:1087-1092.
114. McLeod M, Choudhary S, Giannakakis G, Nouri K. Surgical treatments for lentigo maligna: a review. *Dermatol Surg.* 2011;37:1210-1228.
115. Clayton BD, Leshin B, Hitchcock MG, Marks M, White WL. Utility of rush paraffin-embedded tangential sections in the management of cutaneous neoplasms. *Dermatol Surg.* 2000;26:671-678.
116. Zitelli JA, Brown C, Hanusa BH. Mohs micrographic surgery for the treatment of primary cutaneous melanoma. *J Am Acad Dermatol.* 1997;37:236-245.
117. Bene NI, Healy C, Coldiron BM. Mohs micrographic surgery is accurate 95.1% of the time for melanoma in situ: a prospective study of 167 cases. *Dermatol Surg.* 2008;34:660-664.
118. Hill DC, Gramp AA. Surgical treatment of lentigo maligna and lentigo maligna melanoma. *Australas J Dermatol.* 1999;40:25-30.
119. Malhotra R, Chen C, Huigol SC, Hill DC, Selva D. Mapped serial excision for periocular lentigo maligna and lentigo maligna melanoma. *Ophthalmology.* 2003;110:2011-2018.
120. Mahoney MH, Joseph M, Temple CL. The perimeter technique for lentigo maligna: an alternative to Mohs micrographic surgery. *J Surg Oncol.* 2005;91:120-125.
121. Jejurikar SS, Borschel GH, Johnson TM, Lowe L, Brown DL. Immediate, optimal reconstruction of facial lentigo maligna and melanoma following total peripheral margin control. *Plast Reconstr Surg.* 2007;120:1249-1255.
122. Lee MR, Ryman WJ. Treatment of lentigo maligna with total circumferential margin control using vertical and horizontal permanent sections: a retrospective study. *Australas J Dermatol.* 2008;49:196-201.

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Primary immunodeficiency update

Part I. Syndromes associated with eczematous dermatitis

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Learning Objectives

After completing this learning activity participants should be able to differentiate the new primary immunodeficiency syndromes based on their cutaneous and systemic infection profile.

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In the past decade, the availability of powerful molecular techniques has accelerated the pace of discovery of several new primary immunodeficiencies (PIDs) and revealed the biologic basis of other established PIDs. These genetic advances, in turn, have facilitated more precise phenotyping of associated skin and systemic manifestations and provide a unique opportunity to better understand the complex human immunologic response. These continuing medical education articles will provide an update of recent advances in PIDs that may be encountered by dermatologists through their association with eczematous dermatitis, infectious, and non-infectious cutaneous manifestations. Part I will discuss new primary immunodeficiencies that have an eczematous dermatitis. Part II will focus on primary immunodeficiencies that greatly increase susceptibility to fungal infection and the noninfectious presentations of PIDs. (J Am Acad Dermatol 2015;73:355-64.)

Eczematous dermatitis is a common finding among several primary immunodeficiencies (PIDs) and may be the presenting clinical manifestation to the dermatologist. However, atopic dermatitis is also common in the general population, and the recognition of additional features of immunodeficiency can facilitate an earlier diagnosis. In a series of 75 patients with severe dermatitis with no known underlying primary immunodeficiency, Aghamohammadi

et al¹ identified 5 patients with hyperimmunoglobulin E (IgE) syndrome (HIES) and 1 patient with Wiskott–Aldrich syndrome (WAS). The mean age at diagnosis was 5 years. This underscores the importance of eliciting a history of recurrent infections or family history suggestive of immunodeficiency in patients with severe atopic dermatitis. In this continuing medical education article, we provide an update on primary immunodeficiencies associated with dermatitis.

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HYPERIMMUNOGLOBULIN E SYNDROMES

The first HIES to be described was Job's syndrome. This multisystem PID was initially described in 1966 as a disorder of recurrent cold abscesses, eczematous dermatitis, and lung disease.^{2,3} Autosomal dominant HIES (AD-HIES) shares several clinical features with dedicator of cytokinesis 8 (DOCK8) deficiency, also known as autosomal recessive (AR)-HIES, but also has several key differences that result in distinct phenotypes and prognoses. In addition, there are 2 other rare autosomal recessive diseases associated with HIES. The first is caused by mutations in phosphoglucomutase-3 (*PGM3*). The second disorder, associated with a mutation in tyrosine kinase 2 (*Tyk2*), was reported in 1 patient with elevated IgE levels, eczema, and susceptibility to viral, fungal, and bacterial infections, including mycobacteria.^{4,5} A subsequently reported patient with a mutation in *Tyk2* also had a susceptibility to mycobacterial infections, but did not have HIES, making the link between *Tyk2* mutation and AR-HIES uncertain.^{6,7} Although elevated serum IgE levels and eczematous skin disease is a known presentation among the aforementioned HIES immunodeficiencies, WAS and Netherton syndrome may also present with similar skin and laboratory findings. Fig 1 reviews PIDs associated with eczematous dermatitis and the distinctive features of each syndrome. In this article, we review in greater detail AD-HIES and DOCK8 deficiency and discuss the recently described *PGM3* deficiency.

AUTOSOMAL DOMINANT HYPERIMMUNOGLOBULIN E SYNDROME

Key points

- Early onset dermatitis
- Cold abscesses and lung infections
- Multisystem disease with skeletal and connective tissue abnormalities

In 2007, AD-HIES was found to be caused by dominant negative mutations in the signal transducer and activator of transcription 3 (*STAT3*) gene, a key transcription factor that regulates a diverse number of biologic processes, including cell growth regulation and inflammation.^{8,9}

A majority of patients with AD-HIES develop a neonatal papulopustular eruption (Fig 2, A)—often within the first week of life—that typically begins on the face and scalp, but can generalize. The rash often changes into an eczematous morphology within the

first year.¹⁰ Chronic dermatitis (Fig 2, B) in AD-HIES is strongly associated with *Staphylococcus aureus* skin colonization and infection. Control of *S aureus* through prophylactic systemic antimicrobials and topical antiseptics limits eczematous disease, but recurrences throughout life are common. Exacerbations of dermatitis are often caused by resistant *S aureus* strains or poor antimicrobial adherence. Dilute sodium hypochlorite baths, as used in atopic dermatitis, may be effective, but further clinical study in this population is needed.¹¹ The recommended therapy is a half-cup of household bleach in a full tub of water with exposure for 15 minutes for 3 days each week. For those who are not able or willing to use dilute bleach baths, chlorhexidine- or sodium hypochlorite-containing washes may be helpful.¹² In contrast to DOCK8 and patients with atopic dermatitis with high serum IgE levels, anaphylaxis is rare and food allergies are not a major concern in AD-HIES—although the latter is more prevalent in AD-HIES than in the general population.^{13,14}

S aureus is also the major pathogen responsible for recurrent cold skin abscesses and sinopulmonary infections in patients with AD-HIES. Pulmonary infection results in abscess formation and pneumatocele development (Fig 3, A), which predisposes patients to infection with *Pseudomonas*, *Aspergillus*, and nontuberculous mycobacteria, and additional morbidity. Prophylactic antistaphylococcal antibiotics are recommended to decrease the risk of pneumonia and staphylococcal abscesses.³ Chronic mucocutaneous candidiasis (CMC) occurs in 83% of patients, and many patients require long-term anti-fungal treatment.^{3,10}

STAT3 is integral for the differentiation of T_H17 cells. AD-HIES patients lack T_H17 cells, thereby leading to impaired interleukin (IL)-17/IL-22 signaling and this high risk of CMC.¹⁵ *STAT3* is also important for the production of other proinflammatory cytokines and CD8⁺ T cell memory maintenance, which likely contributes to the risk of reactivation of varicella zoster virus (VZV) and Epstein–Barr virus (EBV).¹⁶ Memory B cell differentiation is also impaired, leading to variable specific antibody production; therefore, some patients require chronic immunoglobulin replacement in addition to prophylactic antimicrobials.¹⁷

As the name implies, elevated serum IgE levels are seen in all patients with AD-HIES, with peak IgE levels above 2000 IU/mL in 97% of patients and eosinophilia in 93%.³ However, IgE levels may diminish over time and be within the normal range in adulthood. Craniofacial, musculoskeletal, and vascular abnormalities are also common and help

Abbreviations used:

AD:	autosomal dominant
AD-HIES:	autosomal dominant hyper-immunoglobulin E syndrome
AR:	autosomal recessive
BMD:	bone mineral density
CMC:	chronic mucocutaneous candidiasis
DOCK8:	dedicator of cytokinesis 8
EBV:	Epstein-Barr virus
FOXP3:	forkhead box protein 3
HIES:	hyper-immunoglobulin E syndrome
HPV:	human papillomavirus
HSCT:	hematopoietic stem cell transplant
HSV:	herpes simplex virus
IDDM:	insulin-dependent diabetes mellitus
IFN:	interferon
IL:	interleukin
IPEX:	immune dysregulation, polyendocrinopathy, and enteropathy, X-linked syndrome
MCV:	molluscum contagiosum virus
MMP:	metalloproteinase
MST1:	mammalian sterile 20-like 1
NK:	natural killer
PGM3:	phosphoglucomutase 3
PID:	primary immunodeficiency
STAT3:	signal transducer and activator of transcription 3
STK4:	serine/threonine protein kinase 4
Treg:	regulatory T
TLR:	Toll-like receptor
TYK2:	tyrosine kinase 2
VZV:	varicella zoster virus
WAS:	Wiskott-Aldrich syndrome

distinguish AD-HIES from other PIDs associated with eczematous dermatitis and skin infection. A characteristic facial appearance emerges in childhood comprised of facial asymmetry, a large bulbous nose, prominent chin, and prominent skin pores (Fig 2, C). Craniosynostosis, Chiari I malformations, retained primary teeth (Fig 3, C), and midline oropharyngeal anomalies are also common, particularly a high-arched palate (Fig 2, D) and midline sagittal cleft of the tongue. Musculoskeletal abnormalities, including scoliosis (Fig 3, B), develop in approximately three-quarters of patients, minimal trauma fractures occur in >50% patients, and joint hyperextensibility is also common (Fig 2, F).^{7,18} Patients with AD-HIES have decreased bone mineral density (BMD) and increased osteoclast activity. Studies in *STAT3* knockout mice confirm an important role for *STAT3* in bone homeostasis¹⁹; however, a recent study did not reveal a relationship between BMD and fracture risk in patients with AD-HIES, as measured on dual-energy x-ray absorptiometry scan or serum markers of osteoclastic activity.¹⁹⁻²¹ *STAT3* is also involved in the regulation of matrix metalloproteinases (MMPs) and plasma levels of

MMP8 and MMP9 are elevated, while MMP3 is lower in patients with AD-HIES. This alteration may be responsible for impaired tissue remodeling.²²

A newly identified systemic manifestation of AD-HIES is vascular anomalies, including lacunar infarcts in the brain, coronary aneurysms (37%), and coronary dilation and tortuosity (70%). The coronary abnormalities have been associated with risk of myocardial infarction.²³⁻²⁵ AD-HIES is also associated with an increased risk of malignancy, most commonly non-Hodgkin's lymphoma.²⁶ Life expectancy for patients with AD-HIES is the fifth to sixth decade. Death is most commonly caused by infection.⁷

DOCK8 DEFICIENCY

Key points

- **Autosomal recessive**
- **Elevated immunoglobulin E and multiple allergies**
- **Eczematous dermatitis**
- **Severe human papillomavirus, molluscum contagiosum virus, and herpes viral infections**

In 2009, mutations in *DOCK8* were identified as the genetic basis in the majority of patients with AR-HIES, a syndrome now commonly referred to as DOCK8 deficiency.^{27,28} Both DOCK8 deficiency and AD-HIES are characterized by elevated serum IgE levels, eosinophilia, eczematous dermatitis, and recurrent sinopulmonary and staphylococcal skin infections. Unlike AD-HIES, DOCK8 deficiency is also characterized by severe cutaneous viral infections caused by herpes simplex virus (HSV; Fig 4, A), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella zoster virus (VZV). Widespread HPV and MCV infection (Fig 4, B-D) may be disfiguring and resistant to standard treatments. Interferon-alpha (IFN α) has been used to treat the mucocutaneous viral infections, with improvement in HPV infection and, in 1 case, HSV infection.^{29,30} Patients are at elevated risk of squamous cell carcinoma at sites of HPV infection (Fig 4, E), and cutaneous T-cell lymphoma has also been reported.^{28,31} Malignancy is a frequent cause of death in the second and third decade of life.^{7,32}

DOCK8 deficiency is associated with impaired natural killer (NK) cell development and survival, which likely contributes to the profound susceptibility to cutaneous viral infections.³³ In addition, CD4 $^{+}$ and CD8 $^{+}$ T cells are frequently reduced and often diminish further with age. Further, plasmacytoid dendritic cells are profoundly

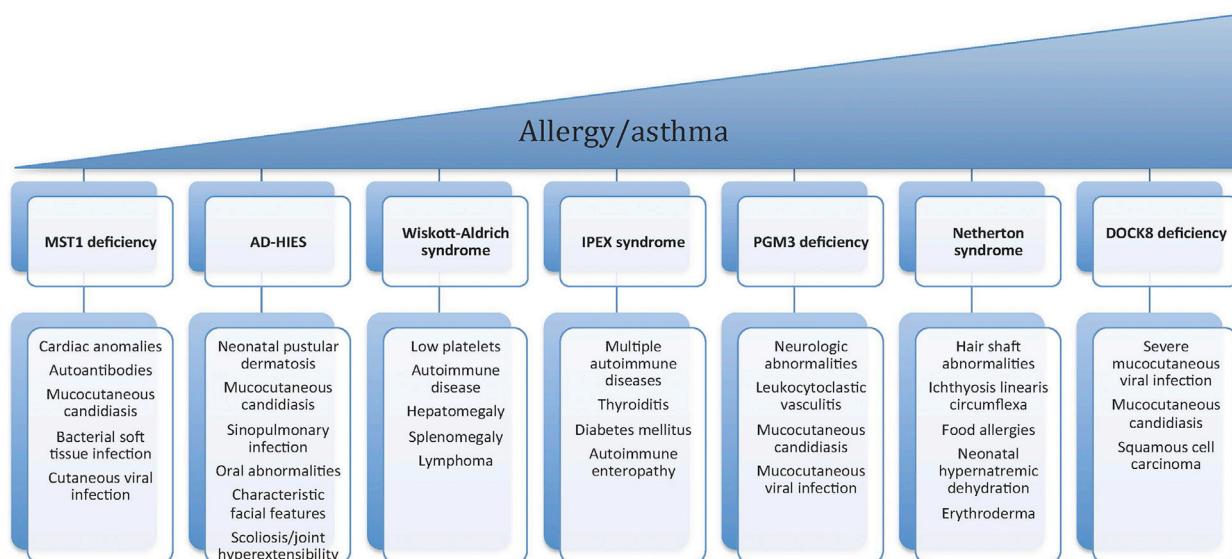


Fig 1. Clinical features of primary immunodeficiencies with eczematous dermatitis stratified by prevalence of allergies and asthma.



Fig 2. Cutaneous findings in autosomal dominant hyperimmunoglobulin E syndrome. **A**, A 3-week-old infant with neonatal pustular eruption of the face. **B**, A 7-year-old boy with chronic dermatitis on the lower back. **C**, Characteristic facies with coarse facial features, a broad nasal bridge, a large bulbous nose, prominent skin pores, and prognathism in a 44-year-old woman. **D**, High arched palate. **E**, Gorlin sign showing hyperextensibility similar to that seen in patients with Ehlers–Danlos syndrome. **F**, Joint hyperextensibility in a 6-year-old boy.

decreased. This cell population is critical for production of IFN α in response to the cutaneous viral infections through the Toll-like receptor (TLR)-9

signaling pathway.^{29,30} Consistent with an elevated risk of recurrent sinopulmonary infections, memory B cells are often reduced in number, and, although

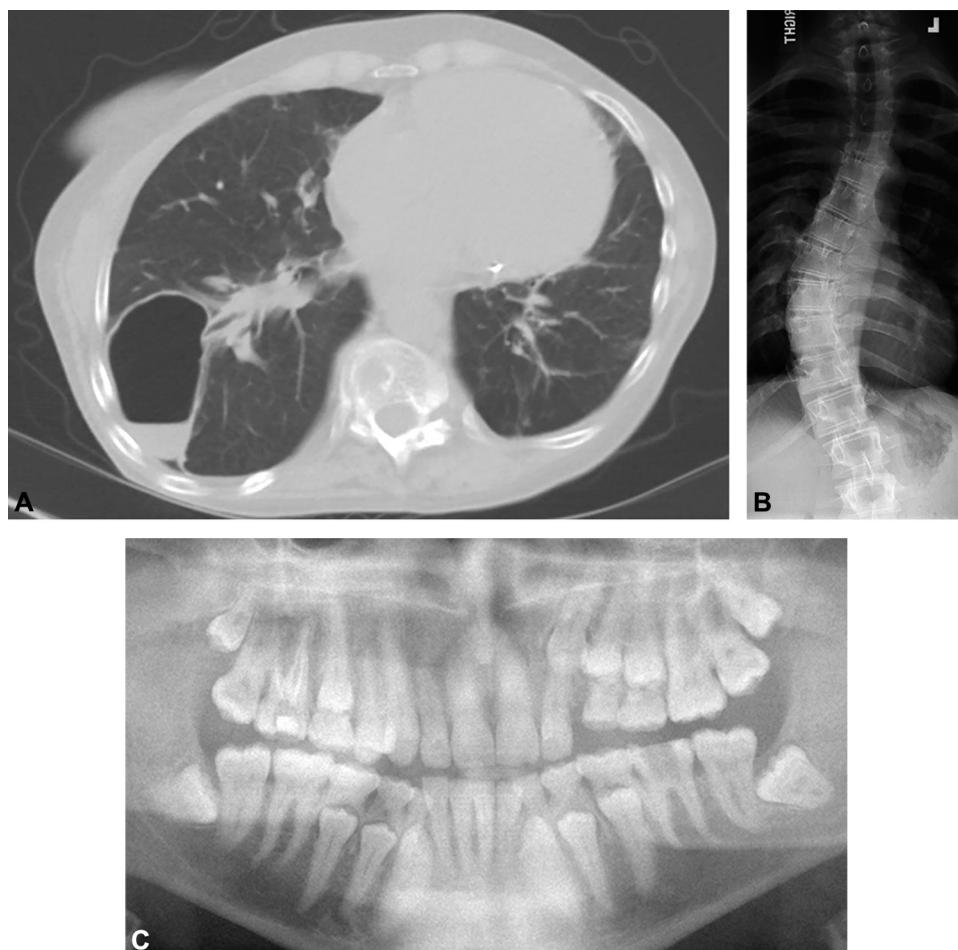


Fig 3. Radiographic findings of patients with autosomal dominant hyperimmunoglobulin E syndrome. **A**, A 42-year-old woman with right lung pneumatocele and **(B)** severe scoliosis. **C**, Multiple retained primary teeth visualized by panoramic radiograph in a 21-year-old man.

total serum IgG levels may be within normal range, specific antibody production is frequently impaired.^{17,34,35} Mucocutaneous candidiasis is less common in DOCK8 deficiency when compared to AD-HIES. Differentiation of T_H17 cells and IL-17 production is impaired, albeit to a lesser degree than seen in AD-HIES.³⁶ The mechanism is not yet understood, but may be related to general T cell deficiency.

Patients with DOCK8 deficiency present with variable severity of dermatitis (Fig 4, F and G). Signs begin in the first several months of life with a classic atopic dermatitis distribution and appearance.³¹ In contrast, most patients with AD-HIES present with a neonatal pustular eruption that eventually progresses to an eczematous dermatitis.¹⁰ In addition, patients with DOCK8 deficiency frequently have multiple food allergies and asthma.

Treatment of the atopic dermatitis is often difficult because of concurrent cutaneous viral infections and a predilection for bacterial infections that can worsen with the use of topical or systemic corticosteroids. Skin superinfection with *S aureus* is frequent, and antiseptic measures, including dilute sodium hypochlorite baths and systemic antibiotics, are recommended based on studies in the general atopic dermatitis population and our experience with dermatitis in the setting of PIDs.^{11,37}

Given the risk of malignancy (squamous cell carcinoma and lymphoma) and the reduced life expectancy associated with DOCK8 deficiency, allogeneic hematopoietic stem cell transplant (HSCT) is the treatment of choice.^{38,39} Cutaneous viral infections and dermatitis have shown dramatic improvement in the first 6 months posttransplant.^{31,40}



Fig 4. The spectrum of cutaneous findings in DOCK8 immunodeficiency. **A**, Severe herpetic stomatitis in a 7-year-old girl. **B**, Generalized molluscum contagiosum with verrucous human papillomavirus infection on the distal fingers of a 22-year-old woman. **C**, Generalized verrucosis of the arm, and **(D)** extensive thin, pink to red brown papules resembling epidermolyticus verruciformis in a 25-year-old man. A biopsy specimen was obtained from the chest, and examination revealed coarse keratohyaline granules and abundant pale gray cytoplasm similar to findings seen in epidermolyticus verruciformis. **E**, A squamous cell carcinoma on the face. **F**, Extensive dermatitis with excoriations and **(G)** postauricular crusting in a 5-year-old with DOCK8 immunodeficiency.

Table I. Comparison of hyperimmunoglobulin E syndromes

	STAT3 deficiency (Job's syndrome)	DOCK8 deficiency	PGM3 deficiency
Genetic features			
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Gene	STAT3	DOCK8	PGM3
Protein	Signal transducer and activator of transcription 3	Dedicator of cytokinesis 8	Phosphoglucomutase 3
Function	Mediates cellular responses to interleukins, stem cell factor, and other growth factors	Activates Rho GTPases, cytoskeletal reorganization, cell migration, and phagocytosis	Enzyme catalyzing conversion of GlcNAc-6-P into GlcNAc-1-P
Immunologic features			
Eosinophilia	Common	Common	Common
Allergies	Rare	Common	Common
Asthma	Rare	Common	Common
Sinopulmonary infection	Common	Common	Common
Bronchiectasis	Common	Rare	Less common
Dermatologic features			
Newborn rash	Cephalic papulopustular eruption	—	—
Eczematous dermatitis	Common	Highly variable	Highly variable
Bacterial skin abscesses	Common	Less common	Common
Leukocytoclastic vasculitis	—	—	Common
Mucocutaneous viral infection	Rare	Very common, severe	Occasional reports
Mucocutaneous candidiasis	Common	Less common	Less common
Other features			
Malignancy	SCC (rare)	SCC (vulvar, facial, anal), lymphoma	—
Characteristic facial appearance	Coarse features, asymmetry, broad nasal root, hypertelorism, and prognathism	—	Narrow palpebral fissures
Oral findings	Retained primary dentition, high-arched palate	—	High-arched palate
Joint hyperextensibility	Very common	Rare	Rare
Minimal trauma fractures	Very common	Rare	—
Scoliosis	Very common	—	Rare
Neurologic symptoms	—	—	Conductive hearing loss, ataxia, and myoclonus

DOCK8, Dedicator of cytokinesis 8; GlcNAc-1-P, N-acetylglucosamine-1-phosphate; GlcNAc-6-P, N-acetylglucosamine-6-phosphate; PGM3, phosphoglucomutase 3; SCC, squamous cell carcinoma; STAT3, signal transducer and activator of transcription 3.

PHOSPHOGLUCOMUTASE 3 DEFICIENCY

Key points

- Autosomal recessive
- Elevated immunoglobulin E levels with dermatitis, multiple allergies, and asthma
- Neurologic abnormalities

Phosphoglucomutase 3 (PGM3) deficiency was described in 2014 as a novel autosomal recessive PID associated with atopic dermatitis, recurrent infections, and elevated IgE levels.^{41,42} PGM3 is a protein that catalyzes the conversion of N-acetylglucosamine-6-phosphate (GlcNAc-6-P) into GlcNAc-1-P in the synthesis of uridine diphosphate-GlcNAc, a

critical component of the glycosylation pathway, thereby affecting a wide range of diverse proteins. Atopic dermatitis was a universal feature in all 17 patients described.^{41,42} Similar to DOCK8 deficiency, patients with PGM3 mutations frequently have other prominent atopic features, including asthma and allergies. These patients tended to have susceptibility to viral infections, including cutaneous HSV and MCV, as seen in DOCK8 deficiency. Much like patients with AD-HIES, patients with PGM3 deficiency have sinopulmonary infections, with bronchiectasis and pneumatocele development and skin and soft tissue bacterial infections. Mucocutaneous candidiasis can also develop, although it is not a consistent feature. One unique cutaneous finding in

PGM3 deficiency is leukocytoclastic vasculitis seen in numerous patients. Distinguishing features of AD-HIES, DOCK8 deficiency, and PGM3 deficiency are shown in Table I. In contrast to AD-HIES and DOCK8 deficiency, neurologic impairment is a prominent feature in patients with PGM3 deficiency, and include developmental delay and low IQ (88%), ataxia (88%), dysarthria (63%), myoclonus (63%), sensorineural hearing loss (50%), and electroencephalography abnormalities (38%).⁴¹ Hypomyelination is seen on brain magnetic resonance imaging scans. Common hematologic manifestations include cytopenias, primarily lymphopenia and neutropenia.

IMMUNE DYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED SYNDROME

Key points

- **X-linked recessive**
- **Early onset dermatitis**
- **Multiorgan autoimmune disease caused by the loss of peripheral tolerance**

Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome is an X-linked recessive condition caused by loss of function mutations in forkhead box protein 3 (*FOXP3*). It is characterized by a decreased or absent T regulatory (Treg) cell population and multiorgan autoimmune disease. There is considerable phenotypic variation in patients with IPEX syndrome without an obvious genotype–phenotype correlation.⁴³ Affected males develop autoimmune enteropathy in infancy that can be life-threatening. Patients may also develop insulin-dependent diabetes mellitus (IDDM) and thyroid dysfunction early in life.⁴⁴ Antibodies to organ-specific antigens have been shown in patients with IPEX syndrome, explaining autoimmune manifestations such as IDDM, thyroiditis, cytopenias, hepatitis, and nephritis.⁴⁵ The most common cutaneous finding is eczematous dermatitis.⁴⁶ Other less frequent presentations include psoriasiform dermatitis, erythroderma, urticaria, pemphigoid nodularis, cheilitis, onychodystrophy, and alopecia universalis.^{44,47,48} Elevated IgE levels and eosinophilia are common, as are food allergies. Infections are likely caused by both the immunosuppressive drugs used to manage the autoimmune disease and impaired skin barrier and gut epithelium. Severe disease may lead to mortality in early childhood. HSCT is currently the only curative treatment, although gene therapy is being investigated.^{49,50}

MAMMALIAN STERILE 20-LIKE KINASE 1 DEFICIENCY

Key points

- **Autosomal recessive**
- **Bacterial, viral, and candidal cutaneous infections**
- **Structural cardiac anomalies**

Mammalian sterile 20-like kinase 1 (MST1) deficiency, previously known as serine/threonine protein kinase 4 (STK4) deficiency, is an autosomal recessive PID associated with bacterial and viral infections (ie, HSV, HPV, MCV, and EBV) and mucocutaneous candidiasis. *MST1* encodes a serine–threonine kinase that is ubiquitously expressed but has increased levels in cells of hematopoietic origin.⁵¹ First reported in 2012, 4 consanguineous affected families with MST1 deficiency have now been described.^{51–53} Systemic findings include structural cardiac anomalies (ie, atrial septal defects and patent foramen ovale) and valvular disease.^{52,53} Eczematous dermatitis has been reported but is poorly characterized.⁵³ In addition, multiple autoantibodies, including antinuclear, anticardiolipin, and antineutrophil cytoplasmic antibodies, and autoimmune hemolytic anemia has been described.^{51–53} *Mst1* and *Mst2* were recently found to be important regulators of *Foxp3* expression and Treg development, providing a biologic rationale for the autoimmune manifestations of this condition.^{54,55} Affected patients have a peripheral neutropenia with normal bone marrow maturation and T and B cell lymphopenia. The primary therapeutic intervention for this condition is infection control. Three patients with MST1 deficiency have undergone HSCT, but 2 died within 6 months because of graft versus host disease and infectious complications.⁵³

In conclusion, genetic advances have identified several novel primary immunodeficiencies and allowed better characterization of their cutaneous phenotypic presentations. In part I, we reviewed the clinical characteristics, genetic basis, and immunologic abnormalities in PIDs associated with eczematous dermatitis, including several newly described syndromes. Part II of this continuing medical education article provides an update on other recently described PIDs that are not associated with eczematous dermatitis.

REFERENCES

1. Aghamohammadi A, Moghaddam ZG, Abolhassani H, et al. Investigation of underlying primary immunodeficiencies in patients with severe atopic dermatitis. *Allergol Immunopathol (Madr)*. 2014;42:336–341.

2. Davis SD, Schaller J, Wedgwood RJ. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. *Lancet*. 1966;1:1013-1015.
3. Sowerwine KJ, Holland SM, Freeman AF. Hyper-IgE syndrome update. *Ann N Y Acad Sci*. 2012;1250:25-32.
4. Minegishi Y, Saito M, Morio T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity*. 2006;25:745-755.
5. Minegishi Y, Karasuyama H. Hyperimmunoglobulin E syndrome and tyrosine kinase 2 deficiency. *Curr Opin Allergy Clin Immunol*. 2007;7:506-509.
6. Klicic SS, Hacimustafaoglu M, Boisson-Dupuis S, et al. A patient with tyrosine kinase 2 deficiency without hyper-IgE syndrome. *J Pediatr*. 2012;160:1055-1057.
7. Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. *Dis Markers*. 2010;29:123-130.
8. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007;357:1608-1619.
9. Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007;448:1058-1062.
10. Eberting CL, Davis J, Puck JM, Holland SM, Turner ML. Dermatitis and the newborn rash of hyper-IgE syndrome. *Arch Dermatol*. 2004;140:1119-1125.
11. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009;123:e808-e814.
12. Ryan C, Shaw RE, Cockerell CJ, Hand S, Ghali FE. Novel sodium hypochlorite cleanser shows clinical response and excellent acceptability in the treatment of atopic dermatitis. *Pediatr Dermatol*. 2013;30:308-315.
13. Siegel AM, Stone KD, Cruse G, et al. Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. *J Allergy Clin Immunol*. 2013;132:1388-1396.
14. Boos AC, Hagl B, Schlesinger A, et al. Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. *Allergy*. 2014;69:943-953.
15. Milner JD, Brenchley JM, Laurence A, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008;452:773-776.
16. Siegel AM, Heimall J, Freeman AF, et al. A critical role for STAT3 transcription factor signaling in the development and maintenance of human T cell memory. *Immunity*. 2011;35:806-818.
17. Avery DT, Deenick EK, Ma CS, et al. B cell-intrinsic signaling through IL-21 receptor and STAT3 is required for establishing long-lived antibody responses in humans. *J Exp Med*. 2010;207:155-171.
18. Grimbacher B, Holland SM, Gallin JL, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med*. 1999;340:692-702.
19. Li J. JAK-STAT and bone metabolism. *JAKSTAT*. 2013;2:e23930.
20. Sowerwine KJ, Shaw PA, Gu W, et al. Bone Density and Fractures in Autosomal Dominant Hyper IgE Syndrome. *J Clin Immunol*. 2014;34:260-264.
21. Araya N, Inose H, Kato T, et al. Spinal deformity caused by hyperimmunoglobulin E syndrome. *J Neurosurg Spine*. 2014;21:292-295.
22. Sekhsaria V, Dodd LE, Hsu AP, et al. Plasma metalloproteinase levels are dysregulated in signal transducer and activator of transcription 3 mutated hyper-IgE syndrome. *J Allergy Clin Immunol*. 2011;128:1124-1127.
23. Freeman AF, Kleiner DE, Nadiminti H, et al. Causes of death in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2007;119:1234-1240.
24. Freeman AF, Collura-Burke CJ, Patronas NJ, et al. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. *Pediatrics*. 2007;119:e1121-e1125.
25. Freeman AF, Avila EM, Shaw PA, et al. Coronary artery abnormalities in Hyper-IgE syndrome. *J Clin Immunol*. 2011;31:338-345.
26. Leonard GD, Posadas E, Herrmann PC, et al. Non-Hodgkin's lymphoma in Job's syndrome: a case report and literature review. *Leuk Lymphoma*. 2004;45:2521-2525.
27. Engelhardt KR, McGhee S, Winkler S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol*. 2009;124:1289-1302.e4.
28. Zhang Q, Davis JC, Lamborn IT, et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med*. 2009;361:2046-2055.
29. Keles S, Jabara HH, Reisli I, et al. Plasmacytoid dendritic cell depletion in DOCK8 deficiency: rescue of severe herpetic infections with IFN- α 2b therapy. *J Allergy Clin Immunol*. 2014;133:1753-1755.e3.
30. Al-Zahrani D, Raddadi A, Massaad M, et al. Successful interferon-alpha 2b therapy for unremitting warts in a patient with DOCK8 deficiency. *Clin Immunol*. 2014;153:104-108.
31. Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. *Arch Dermatol*. 2012;148:79-84.
32. Renner ED, Puck JM, Holland SM, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr*. 2004;144:93-99.
33. Crawford G, Enders A, Gileadi U, et al. DOCK8 is critical for the survival and function of NKT cells. *Blood*. 2013;122:2052-2061.
34. Caracciolo S, Moratto D, Giacomelli M, et al. Expansion of CCR4+ activated T cells is associated with memory B cell reduction in DOCK8-deficient patients. *Clin Immunol*. 2014;152:164-170.
35. Speckmann C, Enders A, Woellner C, et al. Reduced memory B cells in patients with hyper IgE syndrome. *Clin Immunol*. 2008;129:448-454.
36. McDonald DR. TH17 deficiency in human disease. *J Allergy Clin Immunol*. 2012;129:1429-1435.
37. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol*. 2010;163:12-26.
38. Bozta H, Karitnig-Weiβ C, Ausserer B, et al. Clinical and immunological correction of DOCK8 deficiency by allogeneic hematopoietic stem cell transplantation following a reduced toxicity conditioning regimen. *Pediatr Hematol Oncol*. 2012;29:585-594.
39. Gatz SA, Benninghoff U, Schütz C, et al. Curative treatment of autosomal-recessive hyper-IgE syndrome by hematopoietic cell transplantation. *Bone Marrow Transplant*. 2011;46:552-556.
40. Ghosh S, Schuster FR, Adams O, et al. Haploididentical stem cell transplantation in DOCK8 deficiency - Successful control of pre-existing severe viremia with a TCRαβ/CD19-depleted graft and antiviral treatment. *Clin Immunol*. 2014;152:111-114.
41. Zhang Y, Yu X, Ichikawa M, et al. Autosomal recessive phosphoglucomutase 3 (PGM3) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and

- neurocognitive impairment. *J Allergy Clin Immunol.* 2014;133:1400-1409.e5.
42. Sassi A, Lazaroski S, Wu G, et al. Hypomorphic homozygous mutations in phosphoglucomutase 3 (PGM3) impair immunity and increase serum IgE levels. *J Allergy Clin Immunol.* 2014;133:1410-1419.e13.
 43. Baris S, Schulze I, Ozen A, et al. Clinical heterogeneity of immunodysregulation, polyendocrinopathy, enteropathy, X-linked: pulmonary involvement as a non-classical disease manifestation. *J Clin Immunol.* 2014;34:601-606.
 44. Barzagli F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. *Front Immunol.* 2012;3:211.
 45. Tsuda M, Torgerson TR, Selmi C, et al. The spectrum of autoantibodies in IPEX syndrome is broad and includes anti-mitochondrial autoantibodies. *J Autoimmun.* 2010;35:265-268.
 46. Martin-Santiago A, Hervas JA, Hervas D, et al. Diagnostic value of the skin lesions in immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. *Pediatr Dermatol.* 2013;30:e221-e222.
 47. Moraes-Vasconcelos D, Costa-Carvalho BT, Torgerson TR, Ochs HD. Primary immune deficiency disorders presenting as autoimmune diseases: IPEX and APECED. *J Clin Immunol.* 2008;28(Suppl 1):S11-S19.
 48. McGinness JL, Bivens MM, Greer KE, Patterson JW, Saulsbury FT. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) associated with pemphigoid nodularis: a case report and review of the literature. *J Am Acad Dermatol.* 2006;55:143-148.
 49. Passerini L, Santoni de Sio FR, Porteus MH, Bacchetta R. Gene/cell therapy approaches for immune dysregulation polyendocrinopathy enteropathy X-linked Syndrome. *Curr Gene Ther.* 2014;14:422-428.
 50. Horino S, Sasahara Y, Sato M, et al. Selective expansion of donor-derived regulatory T cells after allogeneic bone marrow transplantation in a patient with IPEX syndrome. *Pediatr Transplant.* 2014;18:E25-E30.
 51. Crequer A, Picard C, Patin E, et al. Inherited MST1 deficiency underlies susceptibility to EV-HPV infections. *PLoS One.* 2012;7:e44010.
 52. Abdollahpour H, Appaswamy G, Kotlarz D, et al. The phenotype of human STK4 deficiency. *Blood.* 2012;119:3450-3457.
 53. Nehme NT, Pachlopnik Schmid J, Debeurme F, et al. MST1 mutations in autosomal recessive primary immunodeficiency characterized by defective naive T-cell survival. *Blood.* 2012;119:3458-3468.
 54. Du X, Shi H, Li J, et al. Mst1/Mst2 Regulate Development and Function of Regulatory T Cells through Modulation of Foxo1/Foxo3 Stability in Autoimmune Disease. *J Immunol.* 2014;192:1525-1535.
 55. Tomiyama T, Ueda Y, Katakai T, Kondo N, Okazaki K, Kinashi T. Antigen-specific suppression and immunological synapse formation by regulatory T cells require the Mst1 kinase. *PLoS One.* 2013;8:e73874.

Primary immunodeficiency update

Part II. Syndromes associated with mucocutaneous candidiasis and noninfectious cutaneous manifestations

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Learning Objectives

After completing this learning activity, participants should be able to differentiate the new primary immunodeficiency syndromes based on the noninfectious manifestations (dermatitis, SCC, DFSP, granuloma, cutaneous lupus) that may occur on the skin.

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Editors

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Several primary immunodeficiencies (PIPs) have recently been described that confer an elevated risk of fungal infections and noninfectious cutaneous manifestations. In addition, immunologic advances have provided new insights into our understanding of the pathophysiology of fungal infections in established PIPs. We reviewed PIPs that present with an eczematous dermatitis in part I. In part II of this continuing medical education article we discuss updates on PIPs associated with fungal infections, their biologic basis in PIPs, and noninfectious cutaneous manifestations. (J Am Acad Dermatol 2015;73:367-81.)

Part I of this continuing medical education article addressed primary immunodeficiencies (PIPs) associated with eczematous dermatitis. In part II, we provide an update on other PIPs, including those associated with mucocutaneous candidiasis and PIPs with noninfectious skin manifestations.

NEW MUCOCUTANEOUS CANDIDIASIS SYNDROMES

Key points

- Several new monogenic disorders have been associated with chronic mucocutaneous candidiasis

- Gain of function *STAT1* mutations cause chronic mucocutaneous candidiasis with a variety of systemic manifestations
- *CARD9* mutations predispose to chronic mucocutaneous candidiasis, invasive fungal infections, and deep dermatophytosis

The innate immune response is the host's first line of defense against fungal infection (Fig 1). Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and C-type lectin receptors, recognize components of pathogens, termed pathogen-associated molecular patterns (PAMPs), which are evolutionarily conserved. TLR2 and TLR4 recognize

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Abbreviations used:

ADA:	adenosine deaminase
AIRE:	autoimmune regulator
AML:	acute myeloid leukemia
APECED:	autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia
APLAID:	autoinflammation and PLC γ 2-associated antibody deficiency and immune dysregulation
APS-1:	autoimmune polyendocrine syndrome type 1
AR:	autosomal recessive
CARD9:	caspase-associated recruitment domain
CLEC7A:	C-type lectin domain family 7, member A
CMC:	chronic mucocutaneous candidiasis
COL1A1-PDGFB:	collagen type I, alpha-1-platelet-derived growth factor subunit beta
CXCL12:	chemokine CXC motif ligand 12
CXCR4:	chemokine CXC motif receptor 4
DFSP:	dermatofibrosarcoma protuberans
DOCK8:	dedicator of cytokinesis 8
EBV:	Epstein-Barr virus
GATA2:	GATA-binding protein 2
GOF:	gain of function
HPV:	human papillomavirus
HSCT:	hematopoietic stem cell transplant
IL:	interleukin
MDS:	myelodysplastic syndrome
MonoMAC:	monocytopenia and mycobacterial infection
MST1:	mammalian sterile 20-like 1
mTEC:	medullary thymic epithelial cell
NIH:	National Institutes of Health
NF- κ B:	nuclear factor-kappa B
NK:	natural killer
OS:	Omenn syndrome
PAMPs:	pathogen-associated molecular patterns
PID:	primary immunodeficiency
PLAID:	PLC γ 2-associated antibody deficiency and immune dysregulation
PLCG2:	phospholipase C, gamma 2
PRR:	pattern recognition receptor
RAG:	recombination activating gene
SCID:	severe combined immunodeficiency disease
SDF-1:	stromal cell-derived factor-1
STAT3:	signal transducer and activator of transcription 3
Treg:	T regulatory
TLR:	Toll-like receptor
TNF:	tumor necrosis factor
WHIM:	warts, hypogammaglobulinemia, immunodeficiency and myelokathexis
WILD:	warts, immunodeficiency, primary lymphedema, and anogenital dysplasia

O-linked mannan on the fungal cell wall and activate nuclear factor-kappa B (NF- κ B) through the adaptor protein MyD88. Dectin-1, a C-type lectin receptor, recognizes beta-glucans, leading to NF- κ B induction through the adaptor protein caspase recruitment domain family, member 9 (CARD9). This results in transcription of proinflammatory cytokines that bind to receptors on T_H17 cells. The discovery of T_H17 cells in 2005 and, subsequently, mucocutaneous candidiasis syndromes associated with specific T_H17 signaling defects, highlights the importance of this pathway in host defense to fungi.^{1,2} This has also provided new insight into the pathogenesis of other established PIDs with chronic mucocutaneous candidiasis (CMC; Table I).³

Gain of function *STAT1* mutations

Gain of function (GOF) mutations in signal transducer and activator of transcription 1 (*STAT1*) are associated with autosomal dominant CMC, likely because of a STAT1-dependent increase in the production of interferons (IFNs) that inhibit T_H17 development.³⁻⁵ GOF mutations in *STAT1* result in diminished interleukins (IL)-17A and -22 and an enhanced response to type I IFNs.^{4,6} In addition to CMC, patients are at risk for other fungal infections (eg, disseminated coccidioidomycosis and histoplasmosis), bacterial sinopulmonary infections, mycobacterial, and Herpesviridae family infections.⁷⁻⁹ The clinical severity of this syndrome is highly variable (Fig 2); some patients manifest only CMC, but other patients develop multiple endocrine, dental, gastrointestinal, and autoimmune abnormalities, including early-onset diabetes, enteropathy, hypothyroidism, hemolytic anemia, and autoimmune hepatitis.^{4,10} Cerebral aneurysms and malignancy (oral and esophageal) have also been described.^{4,11}

Dectin-1 mutations

In 2009, Ferwerda et al¹² identified a family with autosomal recessive (AR) CMC associated with mutations in *Dectin-1*. Dectin-1, also known as C-type lectin domain family 7, member A (CLEC7A), is a PRR expressed by phagocytes that recognizes beta-glucans on the fungal cell wall. This protein, along with CARD9, is vital to antifungal immunity via induction of the STAT3 pathway and release of T_H17-differentiating cytokines.^{13,14} Affected patients develop vulvovaginal candidiasis most commonly, followed by oral and esophageal candidiasis, but do not appear to be susceptible to invasive candidal infection. Variants in the *Dectin-1* gene are fairly common; however, the functional significance of these polymorphisms remains unclear.

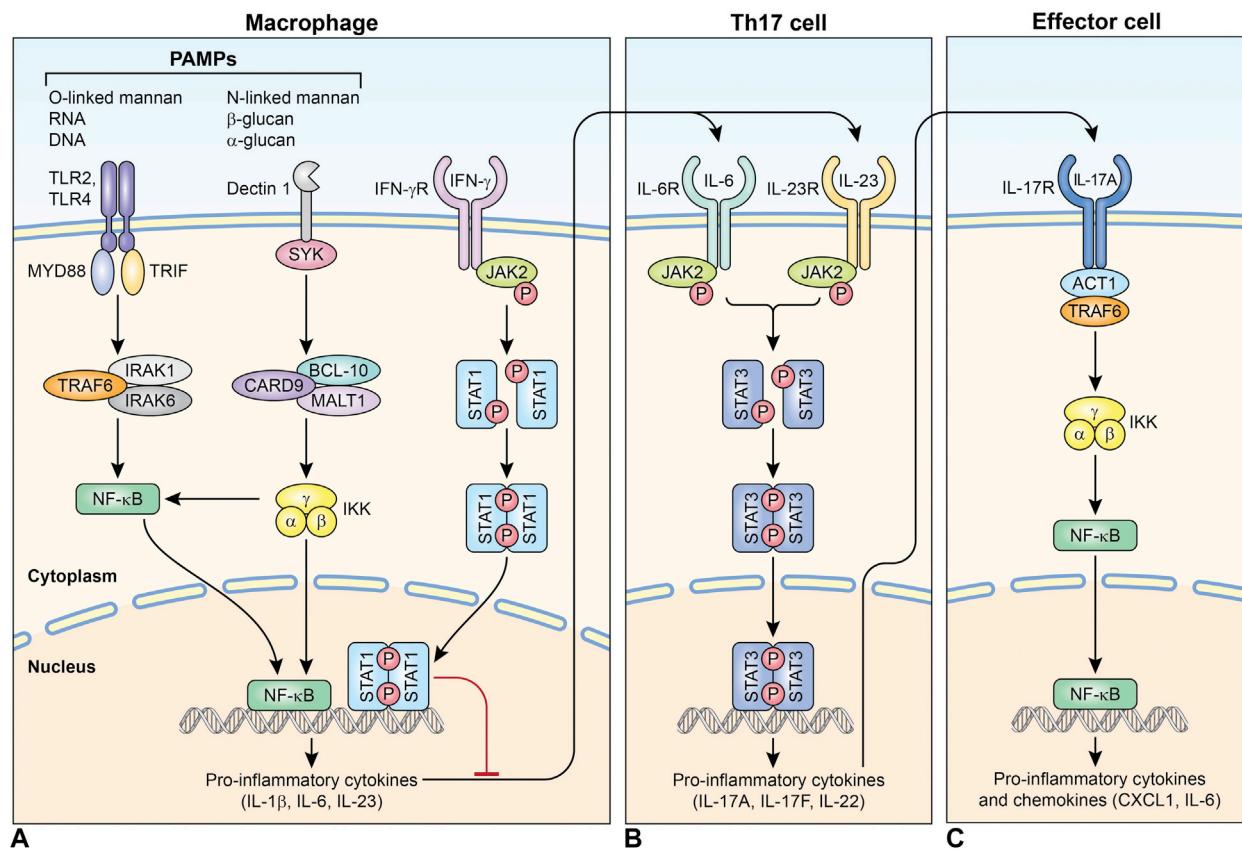


Fig 1. Immune response to fungal infection. **A**, Pattern recognition receptors, such as Toll-like receptors (TLRs) and C-type lectin receptors (eg, Dectin-1) are present on macrophages and dendritic cells and activate independent pathways. TLR2 and TLR4 use the adaptor protein MyD88 to activate nuclear factor-kappa B (NF- κ B). This transcription factor translocates into the nucleus and facilitates the transcription of proinflammatory cytokines. Dectin-1 signals through the adaptor protein caspase recruitment domain family, member 9 (CARD-9), also activating NF- κ B. Binding of interferon- γ (IFN) to its receptor on macrophages allows for homodimerization of signal transducer and activator of transcription 1 (STAT1). This transcription factor produces interferons and proinflammatory cytokines that inhibit T_H17 cell development. **B**, T_H17 cells, which produce cytokines critical for antifungal immunity, signal through STAT3. **C**, IL-17 receptors are expressed on numerous nonhematogenous cells. IL-17 binds its receptor allowing for activation of NF- κ B through the adaptor protein ACT1, producing proinflammatory chemokines and cytokines that are important to the host defense against fungal organisms.

CARD9 deficiency

Mutations in *CARD9* are also responsible for a new monogenic autosomal recessive CMC. However, unlike Dectin-1 deficiency, *CARD9* deficiency is also associated with invasive fungal infection and deep dermatophytosis.^{15,16} Neutrophil dysfunction may account for the invasive potential of fungal infections in *CARD9* deficiency, particularly candidal meningitis.^{17,18} Drewniak et al¹⁷ found that production of IL-6 and -1 β in response to *Candida albicans* is dependent on *CARD9*. The failure of monocytes or dendritic cells to produce these cytokines results in naïve T cells that are unable to differentiate into T_H17 cells.

Recommended therapy for superficial dermatophyte involvement is systemic terbinafine or posaconazole.¹⁹ The addition of granulocyte-macrophage colony-stimulating factor to standard antifungal therapy may improve the therapeutic response to invasive infections.^{20,21}

IL-17RA, IL-17, and ACT1-associated CMC

Three additional recently identified inborn errors of immunity associated with CMC further show the importance of T_H17 cytokines in CMC: autosomal recessive mutations in the *IL-17RA* and *ACT1* genes and autosomal dominant mutations in the *IL-17F* gene. In 2011, Puel et al²² described a boy born to

Table I. Primary immunodeficiencies associated with chronic mucocutaneous candidiasis

PID (inheritance)	Infections (in addition to CMC)	Immunologic abnormalities	Other findings
STAT3/AD hyper-IgE syndrome (AD)	Recurrent cold skin abscesses, sinopulmonary infections, lower respiratory tract infections, and dermatomal herpes zoster	T _H 17 cell deficiency, memory B- and T-cell differentiation impaired, elevated serum IgE level, and eosinophilia	Neonatal papulopustular eruption, eczematous dermatitis, non-Hodgkin lymphoma, craniofacial abnormalities, retained primary teeth, scoliosis, minimal trauma fracture, joint hyperextensibility, and cerebral/coronary artery aneurysms
Gain of function STAT1 mutation (AD)	Sinopulmonary, mycobacterial, and Herpesviridae family infections	Diminished T _H 17 cells and enhanced response to type I IFNs	Insulin-dependent diabetes mellitus, enteropathy, dental enamel abnormalities, hypothyroidism, hemolytic anemia, autoimmune hepatitis, cerebral aneurysm, and oral and esophageal cancer
Dectin-1 mutation (AR)	—	Undetermined	Squamous cell carcinoma
CARD9 deficiency (AR)	Invasive fungal infections, deep dermatophytosis	Impaired T _H 17 differentiation	—
IL-17RA deficiency (AR)	Superficial bacterial skin infections	Abolished response to IL-17A and IL-17F	—
IL-17F deficiency (AD)	—	Impaired IL-17 signaling	—
ACT1 deficiency (AR)	Superficial bacterial skin infections	Abolished response to IL-17A and IL-17F	—
APECED (AR)	—	Autoantibodies to IL-17, IL-22, and type I IFN	Vitiligo, alopecia areata/universalis, hypoparathyroidism, Addison disease, hypothyroidism, autoimmune hepatitis, and pernicious anemia

AD, Autosomal dominant; APECED, autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia; AR, autosomal recessive; CMC, chronic mucocutaneous candidiasis; DM, diabetes mellitus; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; PID, primary immunodeficiency.

consanguineous parents who developed CMC and superficial skin infection with *Staphylococcus aureus* in infancy. Gene sequencing identified a homozygous mutation in the *IL17RA* gene, which encodes the receptor IL-17RA. The same report described a second family with 5 affected family members who developed CMC because of a heterozygous missense mutation in the *IL17F* gene, which encodes IL-17F, one of 6 known IL-17 cytokines. Finally, in 2013, a novel mutation was identified in *ACT1* that results in CMC caused by the loss of response to IL-17.²³ Two siblings were reported with oral thrush and onychomycosis from *Candida* and superficial *S aureus* skin infections. Genetic screening identified biallelic missense mutations in *ACT1*, also known as NF-κB activator 1 or *TRAF3IP2*, encoding an adaptor molecule that interacts with the IL-17 receptors to

allow the downstream activation of pathways, including NF-κB.

AUTOIMMUNE POLYENDOCRINOPATHY, CANDIDIASIS, AND ECTODERMAL DYSPLASIA

Key points

- Autosomal recessive
- Triad of hypoparathyroidism, Addison disease, and CMC
- Autoimmune manifestations common because of the loss of central tolerance

Autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED) is characterized by the triad of CMC, hypoparathyroidism, and Addison disease.¹⁴ Clinical diagnosis requires 2 of

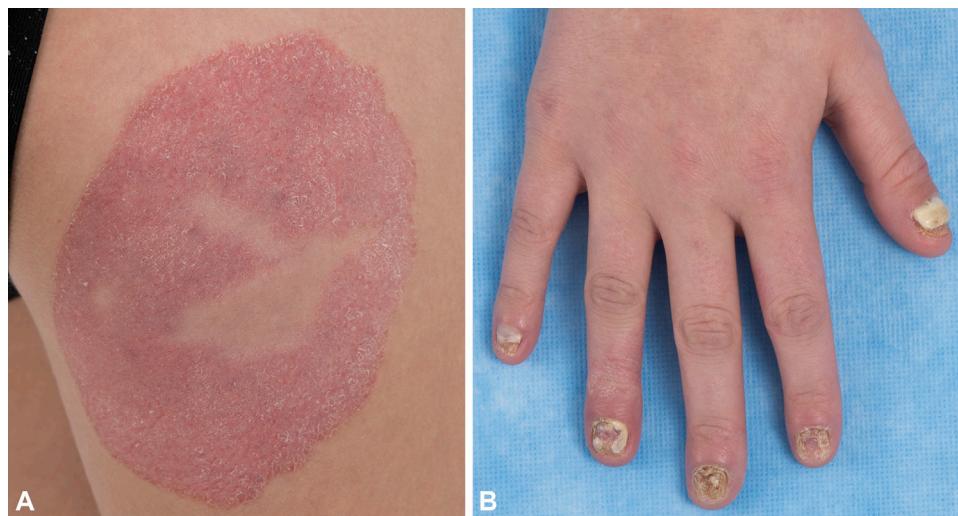


Fig 2. Multiple cutaneous fungal infections associated with *STAT1* gain of function mutation. **A**, *Trichophyton tonsurans* dermatophyte infection on the thigh and **(B)** extensive nail dystrophy caused by a chronic fungal infection in an 18-year-old woman. Nail clippings identified septate hyphae.

these 3 findings; however, additional autoimmune manifestations in the skin and other organs are common. This syndrome, also known as autoimmune polyendocrine syndrome type 1 (APS-1), is a rare autosomal recessive condition caused by biallelic mutations in the autoimmune regulator (*AIRE*) gene.²⁴ *AIRE* is expressed in medullary thymic epithelial cells (mTECs) and is essential for the deletion of autoreactive T cells. Mutations in *AIRE* render the *AIRE* protein undetectable in mTECs and allow the survival of autoreactive T cells.^{25,26} APECED is associated with autoimmune dysfunction of the parathyroid and adrenal glands in early adolescence, hypothyroidism, autoimmune hepatitis, and pernicious anemia.²⁷ Dermatologic manifestations of autoimmunity in APECED include vitiligo and alopecia areata/universalis (Fig 3, A). CMC, often present by 6 years of age, is the primary infectious manifestation in APECED (Fig 3, B). In 2010, autoantibodies against T_H17 cytokines (IL-17A, IL-17F, and IL-22) were discovered in patients with APECED, suggesting a causative link to CMC in these patients.^{26,28,29} A similar susceptibility to CMC caused by autoantibodies to IL-17 and IL-22 has been described in patients with thymoma.²⁶

Granulomatous skin disease in PID

Noninfectious granulomatous skin inflammation is an important cutaneous clue to the diagnosis of PID. Phospholipase C, gamma 2 (PLC γ 2)—associated antibody deficiency and immune dysregulation (PLAID) and severe combined immunodeficiency (SCID) caused by hypomorphic recombination-

activating gene (*RAG*) mutations are recent additions to the differential diagnosis of PIDs associated with noninfectious granulomas (Table II).

PLC γ 2-ASSOCIATED ANTIBODY DEFICIENCY AND IMMUNE DYSREGULATION (PLAID)

Key points

- Autosomal dominant
- Evaporative cold urticaria in all patients, granulomas in a subset of patients
- Neonatal nasal and acral inflammatory lesions

Familial atypical cold urticaria was first described in 2009 in 3 families.³⁰ In 2012, 3 additional unrelated families with evaporative cold urticaria were identified and found to have a genomic deletion in *PLCG2* leading to GOF of the protein PLC γ 2—a syndrome termed PLAID.³¹ PLAID is an autosomal dominant condition that is associated with urticaria induced by evaporative cooling or contact with cold air. Cold urticaria develops in early childhood and persists into adulthood. In this syndrome, PLC γ 2 enzyme activity increases with cold temperature, leading to increased mast cell degranulation. A subset of patients with PLAID also develop neonatal skin lesions on the fingers, toes, and nasal tip. Although the nature of the lesions is not yet fully characterized, nasal lesions have progressed to nasal destruction in 2 cases.³² In addition, a minority of patients with neonatal skin lesions progress to granulomatous skin disease later in life (Fig 4). Patients also develop allergic disease (56%), recurrent sinopulmonary



Fig 3. Autoimmune polyendocrinopathy candidiasis and ectodermal dysplasia. **A**, A 38-year-old man with alopecia universalis, vitiligo, and nail dystrophy (**B**) caused by recurrent candidal infection beginning at 3 years of age.

Table II. Primary immunodeficiencies associated with granuloma formation

Ataxia-telangiectasia
Common variable immunodeficiency
Chronic granulomatous disease
Nijmegen breakage syndrome
PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID)
Hypomorphic <i>RAG</i> mutation

infections (44%), and autoimmune disease (26%), including vitiligo, thyroiditis, and arthritis. Elevated antinuclear antibody titers were found in 62% of patients with PLAID who were tested. Immune abnormalities in PLAID include elevated immunoglobulin E (IgE), decreased IgA and IgM, and decreased circulating B cells and natural killer (NK) cells. B cells in PLAID have reduced class-switched antibody production but an increased mature B cell compartment.³¹

Autoinflammation and PLC γ 2-associated antibody deficiency and immune dysregulation (APLAID), also reported in 2012, is associated with a missense mutation (rather than deletion) in the same gene, *PLCG2*.³³ Patients with APLAID have a more pronounced inflammatory syndrome than patients with PLAID, with recurrent sinopulmonary infections, interstitial pneumonitis and respiratory bronchiolitis, eye inflammation, colitis, and arthralgias. Skin features include epidermolysis bullosa-like blistering in infancy that develops into vesiculopustular lesions and erythematous plaques after exposure to heat. The immunophenotype of APLAID reveals an absence of class-switched memory B cells, as seen in PLAID, with normal naïve and memory T cells and NK cells.³³



Fig 4. Granuloma formation in PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID) syndrome. Widespread granulomatous disease in a 21-year-old with PLAID syndrome. Histopathology revealed sarcoid-like granulomas without central necrosis and diffuse, superficial dermal granulomatous inflammation.

SEVERE COMBINED IMMUNODEFICIENCY

Key points

- Most common cause is a mutation in *IL-2R γ*
- Hypomorphic *RAG* mutations are associated with granulomatous skin disease, autoimmunity, and a less severe infection profile than null *RAG*-associated SCID
- Adenosine deaminase deficient SCID patients are at risk of single or multiple dermatofibrosarcoma protuberans tumors

SCID is a group of disorders characterized by B- and T cell immunodeficiency and multiple known genetic defects. The most common form is X-linked recessive SCID, caused by mutations in the *IL-2R γ* gene. This produces a T⁻B⁺NK⁻ immunophenotype with early onset infection and risk of death; however, many other phenotypes have recently been described with variable presentations.

Null mutations in *RAG1* or *RAG2* are responsible for about 20% of cases of SCID. These genes play a critical role in recombination of V(D)J segments of immunoglobulins and T cell receptors. This is important both for antigen recognition and maturation of lymphocytes.³⁴ It has long been recognized that null mutations of this gene are responsible for classic autosomal recessive T⁻B⁻NK⁺ SCID. This leads to severe early-onset viral and bacterial infections, usually within the first month of life. A hematopoietic stem cell transplant (HSCT) is often necessary for survival.

In contrast to patients with null mutations, patients with hypomorphic *RAG* mutations have residual V(D)J recombination with variable clinical presentations.³⁵ The clinical spectrum of hypomorphic RAG SCID now includes the following: (1) Omenn syndrome (OS); (2) early-onset autoimmunity; (3) immunodeficiency with granulomas; (4) isolated CD4⁺ lymphopenia; and (5) cytomegalovirus infection with γδ T cell expansion.³⁶⁻⁴⁰ OS was the first characterized syndrome associated with hypomorphic *RAG* mutations, and presents similar to classic SCID with infections early in infancy. The immunophenotype is T^{+/−}B⁻NK⁺. Patients develop erythroderma in infancy, lymphadenopathy, hepatosplenomegaly, and alopecia. Laboratory evaluation in OS reveals eosinophilia, elevated serum IgE, an absence of B cells, and expansion of oligoclonal T cells that infiltrate organs.^{34,36,41} This condition may be fatal despite early HSCT.³⁶

In 2008, Schuetz et al³⁶ reported a new presentation of hypomorphic mutations in *RAG1* or *RAG2*, characterized by granulomatous skin disease early in life, but a less severe immunodeficiency than null mutation RAG SCID. The immunophenotype in these patients is T^{+/−}B^{+/−}NK⁺, with low lymphocyte counts and low immunoglobulin levels, including IgE.³⁶ Destructive granulomas developed in the skin and visceral organs and responded poorly to treatments, including corticosteroids and antibiotic and immunosuppressant medications.^{35,36,42,43} It has been postulated that these destructive granulomas are a result of a dysregulated hyperinflammatory response to viral antigens.

Adenosine deaminase (ADA) deficiency is the most common cause of AR SCID. The immunophenotype is notable for profound cytopenia of T, B, and NK cells and impairment of both cellular and humoral immunity. ADA plays a key role in the purine salvage pathway, and ADA deficiency leads to the accumulation of toxic metabolites and eventual chromosomal breakage.⁴⁴ ADA-SCID is associated with a high rate of mortality, and most patients present in the neonatal or infantile period with

severe fungal, viral, and bacterial infections.⁴⁵ However, the use of pegylated ADA enzyme replacement and gene therapy has dramatically altered the life expectancy in this severe immunodeficiency.

An association between ADA-SCID and dermatofibrosarcoma protuberans (DFSP) has been recently reported. Kesserwan et al⁴⁶ found that 8 of 12 patients with ADA-SCID followed at the National Institutes of Health (NIH) had ≥1 DFSP lesions (including 15 lesions in 1 patient). The majority of tumors presented as atrophic plaques located on the trunk and extremities (Fig 5, A and B). Patient age at the time that the biopsy was performed ranged from 2 to 22 years. ADA-SCID-associated DFSP lesions have a proliferation of CD34⁺ spindle cells but often lack the prototypic storiform histologic appearance (Fig 5, C-E). In this cohort, lesions were confirmed by molecular testing to harbor the characteristic collagen type I, alpha-1 platelet-derived growth factor subunit beta (COL1A1-PDGFB) fusion gene found in DFSP tumors. The natural history of ADA-SCID DFSP is unknown; the optimal management strategy is also unclear. Given the multiplicity of lesions in affected patients, wide excision of lesions would require numerous, potentially disfiguring surgical procedures. The potential role of imatinib mesylate for management of ADA-SCID DFSPs has not been studied in this setting.

PID associated with human papillomavirus infection

Cutaneous viral infections, such as human papillomavirus (HPV), are a common presentation of numerous recently described PIDs: DOCK8 deficiency and MST1 deficiency (see part I), GOF STAT1 mutation, GATA2 deficiency, and warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome, which will be discussed below (Table III). A history of widespread or treatment-refractory disease and a careful family history can identify patients who are at risk for an underlying PID and who may require close surveillance for HPV-related dysplasia and malignancy.

GATA2 DEFICIENCY

Key points

- Autosomal dominant
- Human papillomavirus infection with frequent progression to dysplasia
- Variable age of onset of infections
- High risk of myelodysplasia/acute myeloid leukemia

In 2011, loss of function mutations in GATA-binding protein 2 (*GATA2*) were found to be

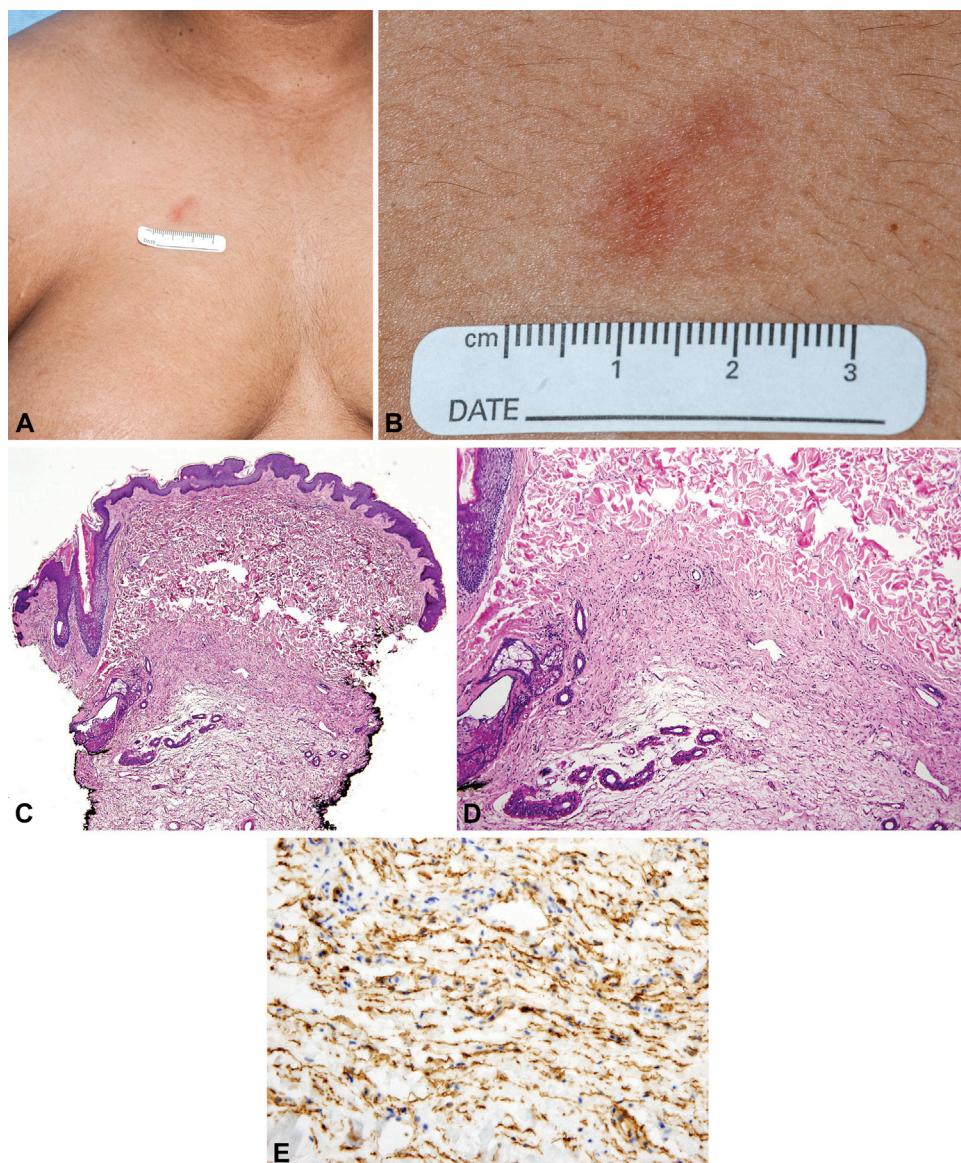


Fig 5. Multiple dermatofibrosarcoma protuberans in a patient with adenosine deaminase (ADA)—severe combined immunodeficiency disease (SCID). **A**, Irregularly shaped red-brown plaque on the upper aspect of the chest in a 17-year-old male with ADA-SCID. **B**, A depressed atrophic plaque with poorly defined margins is seen on close examination. **C**, Histopathologic analysis from 3 similar lesions on this patient revealed a spindle cell infiltrate, primarily in the reticular dermis (**D**). **E**, Immunohistochemistry revealed that the spindle cell infiltrate strongly expressed CD34; reverse transcription polymerase chain reaction studies from the specimen found the presence of COL1A1/PDGFB fusion transcripts. (**C** and **D**, Hematoxylin–eosin stain; **E**, CD34 stain; original magnifications: **C**, $\times 40$; **D**, $\times 100$; **E**, $\times 200$.)

responsible for 4 syndromes: (1) monocytopenia and mycobacterial infection (MonoMAC) syndrome; (2) dendritic cell, monocyte, B lymphocyte, and NK lymphocyte deficiency; (3) familial myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML); and (4) Emberger syndrome (primary lymphedema and MDS; **Table IV**).^{47–52} GATA2, one of 6 known mammalian GATA factors, is a zinc-finger transcription factor expressed in hematopoietic stem cells.

The variety of functions of this gene, including regulation of other transcription factors, lymphatic development, endothelial cell activation, and proliferation, explains the diverse clinical findings of GATA2 deficiency (**Fig 6**).⁴⁷ In 2014, a cohort of 57 patients with GATA2 deficiency was reported from the NIH, demonstrating remarkable disease heterogeneity in age of onset (early childhood to late adulthood) and disease severity.⁵³ Kindred studies

Table III. New primary immunodeficiencies associated with viral infections

Immunodeficiency	Noninfectious cutaneous manifestation(s)	Infection predisposition	Immunologic abnormalities	Other associated findings
GATA2 deficiency	Panniculitis, congenital lymphedema, melanoma, and nonmelanoma skin cancer	HPV, HSV, VZV, NTM, and severe <i>Clostridium difficile</i> infections	Monocyte, B, and NK cell cytopenia, dendritic cell cytopenias, variable CD4 ⁺ lymphopenia, variable neutropenia, and normal immunoglobulins	MDS, leukemia, thromboembolic disorder, PAP, sensorineural hearing loss, and thyroid disease
WHIM syndrome		Bacterial pneumonia, sinusitis, skin/soft tissue infection, HPV, HSV, EBV, and VZV	Neutropenia, B and T cell lymphopenia, decreased IgG and IgA, normal IgM and antibody response	B cell lymphoma, EBV-lymphoproliferative disorder, structural cardiac anomalies, and upper limb anomalies
DOCK8 deficiency	Eczematous dermatitis and squamous cell carcinoma	Bacterial pneumonia, sinusitis, skin/soft tissue infection, HPV, HSV, MCV, and VZV	Variable B, T, and NK cell cytopenia, eosinophilia, elevated IgE levels, normal/elevated IgG and IgA levels, decreased IgM levels, and variable antibody response	Asthma, allergies, lymphoma, and EBV-lymphoproliferative disorder
MST1 deficiency	Eczematous dermatitis	Bacterial pneumonia, sinusitis, skin/soft tissue infection, HPV, HSV, MCV, and VZV	Neutropenia and B and T cell lymphopenia	EBV-lymphoproliferative disorder, structural cardiac anomalies, and autoimmunity
Gain of function STAT1 mutation		Bacterial sinopulmonary, mycobacterial infection, HSV, EBV, VZV, CMV, mucocutaneous candidiasis, and disseminated fungal infection	Diminished T _H 17 cells and enhanced response to type I interferons	Endocrine abnormalities, dental enamel abnormalities, autoimmunity, cerebral aneurysm, and oral and esophageal malignancy

CMV, Cytomegalovirus; DOCK8, dedicator of cytokinesis 8; EBV, Epstein-Barr virus; GATA2, GATA-binding protein 2; HPV, human papillomavirus; HSV, herpes simplex virus; Ig, immunoglobulin; MCV, molluscum contagiosum virus; MDS, myelodysplastic syndrome; MST1, mammalian sterile 20-like 1; NK, natural killer; NTM, nontuberculosis mycobacteria; PAP, pulmonary alveolar proteinosis; STAT1, signal transducer and activator of transcription 1; VZV, varicella zoster virus; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis.

have shown that affected family members may manifest limited signs and symptoms. Therefore, genetic screening is recommended for all family members so that appropriate clinical screening can be performed.

Infection and myelodysplasia are often the presenting signs of GATA2 deficiency and were found in 82% and 84% of the patients in the NIH cohort, respectively.⁵³ The most common infection is HPV, reflecting the profound NK cytopenia and dysfunction characteristic of GATA2 deficiency. HPV infection usually presents by the second decade of life and manifests as generalized verrucosis with persistent cutaneous and genital disease that can rapidly progress to cervical,

vulvar, and anal dysplasia (Fig 7, A).⁴⁹ Other common infections include disseminated non-tuberculous mycobacteria (Fig 7, B), severe cutaneous and systemic bacterial infections, Herpesviridae family infections, and fungal infections. Mycobacterial and fungal infections generally present in the third decade of life.⁴⁹ HPV infection is often recalcitrant to treatment, but IFN α and IFN γ have been successful in several patients.^{54,55} Azithromycin is recommended as prophylaxis against nontuberculous mycobacterial infection, and early HPV vaccination should be considered—although no studies on the efficacy of vaccination have been performed in the setting of GATA2 deficiency.⁵³

Table IV. Syndromes associated with GATA2 mutations

GATA2-related syndrome	Immunologic findings	Infections	Other clinical findings
MonoMac syndrome	Monocyte, B, and NK cell cytopenia	Mycobacterial, fungal, and viral	Pulmonary alveolar proteinosis, erythema nodosum, lymphedema, myelodysplasia, and myeloid leukemia
DCML deficiency	Dendritic cell, monocyte, B and NK cell cytopenia	Mycobacterial and viral	Pulmonary alveolar proteinosis, myelodysplasia, and myeloid leukemia
Familial myelodysplastic syndrome/acute myeloid leukemia	Multilineage cytopenia	—	Myelodysplasia and myeloid leukemia
Emberger syndrome	Variable multilineage cytopenia	Viral	Congenital sensorineural hearing loss, lower limb and genital primary lymphedema, anogenital dysplasia, myelodysplasia, and myeloid leukemia

DCML, Dendritic cell, monocyte, B and NK lymphoid; MonoMac, monocytopenia and mycobacterial infection; NK, natural killer.

Patients with GATA2 deficiency develop autoimmunity through mechanisms that are not yet fully understood. Autoimmune thyroid disease is most frequent, and was found in 8 of 57 patients followed at the NIH (14%).⁵³ Decreased regulatory T (Treg) cells may promote autoimmunity. In addition, CD56^{bright} NK cells play an immunoregulatory role, and therefore absence of this NK subtype may predispose patients with GATA2 deficiency to autoimmunity.^{55,56}

GATA2 deficiency is also associated with pulmonary alveolar proteinosis (18%), which can lead to pulmonary arterial hypertension (9%). Panniculitis, including erythema nodosum (Fig 7, C), develops in one-third of patients with GATA2 deficiency and is frequently associated with underlying infection, particularly mycobacterial infection. Eleven percent of patients in the NIH cohort also developed unilateral or bilateral lymphedema, and one-quarter developed venous thromboses.⁵³

Malignancy is a major cause of morbidity and mortality in GATA2 deficiency. One-third of patients develop HPV-related dysplasia and 11% of patients in the NIH cohort developed melanoma or nonmelanoma skin cancer.⁵³ Breast cancer and other solid tumors were also identified in the NIH cohort; however, the greatest risk of death for patients with GATA2 deficiency is progression of MDS to AML and chronic myelomonocytic leukemia. Patients with GATA2 deficiency have an approximately 50% risk of developing MDS or leukemia in early adulthood, and an early diagnosis can therefore be lifesaving.^{50,57} Myelodysplasia, present in 84% of GATA2 patients in the NIH cohort, results in multilineage cytopenia

of B cells, NK cells, monocytes, and dendritic cells. In addition, there is variable CD4⁺ lymphocytopenia and neutropenia.^{53,58} In 1 recent study of patients carrying a clinical diagnosis of idiopathic cyclic neutropenia or CD4⁺ lymphocytopenia, GATA2 mutations were found in 6 of 14 patients screened.⁵⁹ HSCT offers the only cure for GATA2 deficiency.^{53,57}

WILD syndrome, an acronym for a syndrome of disseminated warts, immunodeficiency, primary lymphedema, and anogenital dysplasia, was proposed by Kreuter et al⁶⁰ in 2008. This group identified 1 previously reported case with similar findings to their patient.⁶¹ However, given the similarity between the clinical features between these presentations, it is suspected that the reported patients with WILD syndrome may have GATA2 deficiency.⁵⁴

WHIM SYNDROME

Key points

- Autosomal dominant
- Human papillomavirus infections with variable severity
- Recurrent bacterial infections
- Plerixafor offers a potential targeted therapy for WHIM syndrome

WHIM syndrome is a rare autosomal dominant PID that was initially described in 1964 in a 10-year-old girl with recurrent infections and granulocytopenia.⁶² This patient also had a characteristic bone marrow abnormality of WHIM syndrome, myelokathexis, which is retention of neutrophils in the marrow. In 2003, GOF mutations in the gene encoding

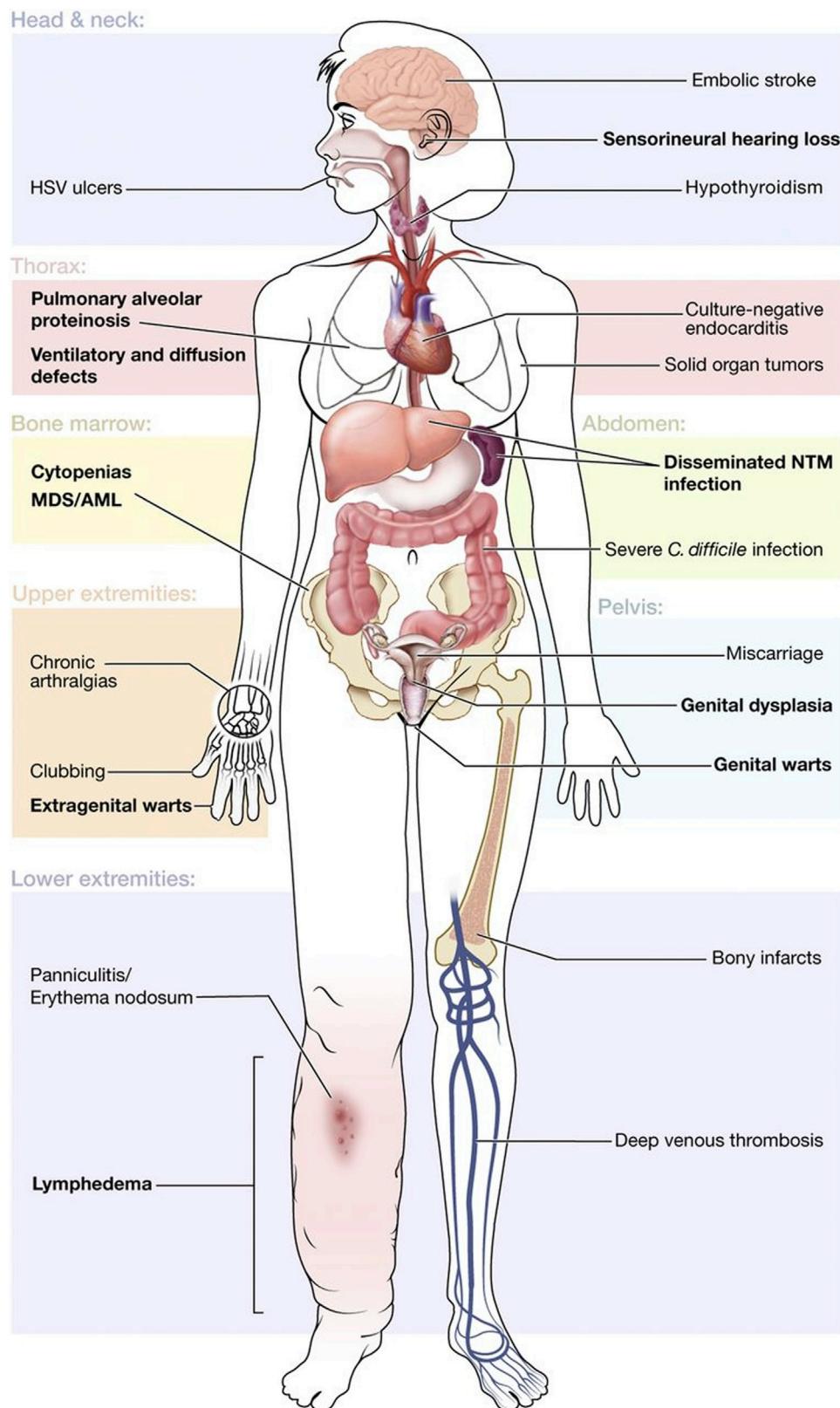


Fig 6. Cutaneous and systemic findings in GATA2 syndrome. Reprinted with permission from Spinner et al.⁸



Fig 7. Cutaneous findings in GATA2 deficiency. **A**, Extensive human papillomavirus infection with vulvar and anal intraepithelial neoplasia; **(B)** cutaneous mycobacterial infection; and **(C)** erythema nodosum—like panniculitis in a 40-year-old woman with GATA2 deficiency.

chemokine (C-X-C motif) receptor 4 (CXCR4) were found to be responsible for this condition.⁶³ CXCR4 is the receptor for chemokine (C-X-C motif) ligand 12 (CXCL12), which regulates hematopoiesis and peripheral trafficking of neutrophils and lymphocyte subsets.⁶³

WHIM syndrome manifests with peripheral neutropenia, hypogammaglobulinemia, and HPV infection.⁶⁴ HPV manifestations range from mild disease with multiple verrucae on the genitals, hands, and feet to severe involvement (Fig 8) with HPV-associated oral and cervical carcinoma. Despite peripheral neutropenia, there is appropriate release of neutrophils from the bone marrow in response to acute infection; therefore, serious bacterial infections are rare. However, hypogammaglobulinemia can lead to recurrent sinopulmonary infections. Unlike many primary immunodeficiencies, autoimmunity and malignancy are infrequent in WHIM syndrome and are limited to a few reports of B cell lymphoma, Epstein–Barr virus (EBV)–associated lymphoproliferative disorder, and cutaneous T cell lymphoma.^{65–67} Other reported systemic findings include tetralogy of Fallot, a double aortic arch, radius hypoplasia, and phalangeal dysgenesis.⁶⁸

The immunodeficiency of WHIM syndrome is primarily a consequence of myelokathexis. Other immunologic abnormalities include lymphocytopenia, affecting B cells more than T cells, delayed antibody class-switching to IgG, and



Fig 8. Warts, hypogammaglobulinemia, immunodeficiency and myelokathexis (WHIM) syndrome. Confluent perianal condyloma and scattered verrucous papules on the buttock of a 4-year-old with WHIM syndrome.

hypogammaglobulinemia.⁶⁹ Reduced plasmacytoid and myeloid dendritic cells at the site of HPV infection may result in reduction of IFN α

production in response to viral infection in patients with WHIM syndrome.^{70,71} CXCR4 is expressed by hematopoietic cells and has been extensively studied as a coreceptor for HIV entry. Both CXCR4 and its ligand CXCL12 (also known as stromal cell-derived factor-1 or SDF-1) are necessary for the development and trafficking of myeloid cells and B lymphocytes.^{63,70} Plerixafor is a small molecule antagonist of CXCR4 that has been approved by the US Food and Drug Administration for hematopoietic stem cell mobilization in patients with non-Hodgkin lymphoma or multiple myeloma. In 2010, 2 phase I trials concluded that plerixafor can effectively mobilize leukocytes from the bone marrow and increase the peripheral absolute lymphocyte, monocyte, and neutrophil counts in patients with WHIM syndrome.^{72,73} These trials and a more recent study in 2014 suggest that this targeted therapy may decrease bacterial infections and HPV burden in patients with WHIM syndrome.⁷²⁻⁷⁴

Prophylactic antibiotic coverage for encapsulated bacteria and *Staphylococcus* is recommended for patients with WHIM syndrome.⁷⁰ The effectiveness of HPV vaccination in WHIM patients is unknown, but given the burden of HPV infection and risk of dysplasia, our recommendation is to offer HPV vaccination early. Replacement gammaglobulin may be needed along with granulocyte colony-stimulating factor for neutropenia. Although mortality in patients with WHIM syndrome is lower than other PIDs, early diagnosis can lead to appropriate prophylactic and treatment strategies to minimize infections and HPV-related dysplasia and malignancy.

In conclusion, the use of powerful molecular tools has ushered in an exciting new era of understanding of the genetic basis of PIDs. This has allowed clear characterization of distinct disease phenotypes, including specific susceptibility to viral and fungal infections and both the infectious and noninfectious cutaneous manifestations of PID. These advances will also continue to advance our ability to effectively manage these rare but potentially devastating conditions.

REFERENCES

1. Park H, Li Z, Yang XO, Chang SH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nature immunology*. 2005;6:1133-1141.
2. Harrington LE, Hatton RD, Mangan PR, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nature immunology*. 2005;6:1123-1132.
3. McDonald DR. TH17 deficiency in human disease. *J Allergy Clin Immunol*. 2012;129:1429-1435.
4. van de Veerdonk FL, Plantinga TS, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011;365:54-61.
5. Liu L, Okada S, Kong XF, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011;208:1635-1648.
6. Yamazaki Y, Yamada M, Kawai T, et al. Two Novel Gain-of-Function Mutations of STAT1 Responsible for Chronic Mucocutaneous Candidiasis Disease: Impaired Production of IL-17A and IL-22, and the Presence of Anti-IL-17F Autoantibody. *J Immunol*. 2014;193:4880-4887.
7. Sampaio EP, Bax HI, Hsu AP, et al. A novel STAT1 mutation associated with disseminated mycobacterial disease. *J Clin Immunol*. 2012;32:681-689.
8. Toth B, Mehes L, Tasko S, et al. Herpes in STAT1 gain-of-function mutation [corrected]. *Lancet*. 2012;379:2500.
9. Uzel G, Sampaio EP, Lawrence MG, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. *J Allergy Clin Immunol*. 2013;131:1611-1623.
10. Frans G, Moens L, Schaballie H, et al. Gain-of-function mutations in signal transducer and activator of transcription 1 (STAT1): Chronic mucocutaneous candidiasis accompanied by enamel defects and delayed dental shedding. *J Allergy Clin Immunol*. 2014;134:1209-1213.e6.
11. Soltesz B, Toth B, Shabashova N, et al. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. *J Med Genet*. 2013;50:567-578.
12. Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med*. 2009;361:1760-1767.
13. Bishu S, Hernandez-Santos N, Simpson-Abelson MR, et al. The adaptor CARD9 is required for adaptive but not innate immunity to oral mucosal *Candida albicans* infections. *Infect Immun*. 2014;82:1173-1180.
14. Kisand K, Peterson P. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and other primary immunodeficiency diseases help to resolve the nature of protective immunity against chronic mucocutaneous candidiasis. *Curr Opin Pediatr*. 2013;25:715-721.
15. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009;361:1727-1735.
16. Lanternier F, Pathan S, Vincent QB, et al. Deep dermatophytosis and inherited CARD9 deficiency. *N Engl J Med*. 2013;369:1704-1714.
17. Drewniak A, Gazendam RP, Tool AT, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. *Blood*. 2013;121:2385-2392.
18. Gazendam RP, van Hamme JL, Tool AT, et al. Two independent killing mechanisms of *Candida albicans* by human neutrophils: evidence from innate immunity defects. *Blood*. 2014;124:590-597.
19. Jachiet M, Lanternier F, Rybojad M, et al. Posaconazole Treatment of Extensive Skin and Nail Dermatophytosis Due to Autosomal Recessive Deficiency of CARD9. *JAMA Dermatol*. 2015;151:192-194.
20. Gavino C, Cotter A, Lichtenstein D, et al. CARD9 Deficiency and Spontaneous Central Nervous System Candidiasis: Complete Clinical Remission With GM-CSF Therapy. *Clin Infect Dis*. 2014;59:81-84.
21. Wildbaum G, Shahar E, Katz R, Karin N, Etzioni A, Pollack S. Continuous G-CSF therapy for isolated chronic mucocutaneous candidiasis: complete clinical remission with restoration of IL-17 secretion. *J Allergy Clin Immunol*. 2013;132:761-764.
22. Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;332:65-68.

23. Boisson B, Wang C, Pedergnana V, et al. An ACT1 Mutation Selectively Abolishes Interleukin-17 Responses in Humans with Chronic Mucocutaneous Candidiasis. *Immunity*. 2013;39:676-686.
24. Björses P, Aaltonen J, Horelli-Kuitunen N, Yaspo ML, Peltonen L. Gene defect behind APECED: a new clue to autoimmunity. *Hum Mol Genet*. 1998;7:1547-1553.
25. Arstila TP, Jarva H. Human APECED; a Sick Thymus Syndrome? *Front Immunol*. 2013;4:313.
26. Kisand K, Lilic D, Casanova JL, Peterson P, Meager A, Willcox N. Mucocutaneous candidiasis and autoimmunity against cytokines in APECED and thymoma patients: clinical and pathogenetic implications. *Eur J Immunol*. 2011;41:1517-1527.
27. Gupta S, Louis AG. Tolerance and autoimmunity in primary immunodeficiency disease: a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45:162-169.
28. Kisand K, Boe Wolff AS, Podkrajsek KT, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med*. 2010;207:299-308.
29. Puel A, Doffinger R, Natividad A, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010;207:291-297.
30. Gandhi C, Healy C, Wanderer AA, Hoffman HM. Familial atypical cold urticaria: description of a new hereditary disease. *J Allergy Clin Immunol*. 2009;124:1245-1250.
31. Ombrello MJ, Remmers EF, Sun G, et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *N Engl J Med*. 2012;366:330-338.
32. Aderibigbe OM, Priel DL, Lee CR, et al. Distinct cutaneous manifestations and cold-induced leukocyte activation associated with PLCG2 mutations. *JAMA Dermatol*. 2015;151:627-634.
33. Zhou Q, Lee GS, Brady J, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase C γ 2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. *Am J Hum Genet*. 2012;91:713-720.
34. Niehues T, Perez-Becker R, Schuetz C. More than just SCID—the phenotypic range of combined immunodeficiencies associated with mutations in the recombinase activating genes (RAG) 1 and 2. *Clin Immunol*. 2010;135:183-192.
35. Avila EM, Uzel G, Hsu A, et al. Highly variable clinical phenotypes of hypomorphic RAG1 mutations. *Pediatrics*. 2010;126:e1248-e1252.
36. Schuetz C, Huck K, Gudowius S, et al. An immunodeficiency disease with RAG mutations and granulomas. *N Engl J Med*. 2008;358:2030-2038.
37. de Villartay JP, Lim A, Al-Mousa H, et al. A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. *J Clin Invest*. 2005;115:3291-3299.
38. Ehl S, Schwarz K, Enders A, et al. A variant of SCID with specific immune responses and predominance of gamma delta T cells. *J Clin Invest*. 2005;115:3140-3148.
39. Kuijpers TW, Ijspeert H, van Leeuwen EM, et al. Idiopathic CD4+ T lymphopenia without autoimmunity or granulomatous disease in the slipstream of RAG mutations. *Blood*. 2011;117:5892-5896.
40. Henderson LA, Frugoni F, Hopkins G, et al. Expanding the spectrum of recombination-activating gene 1 deficiency: A family with early-onset autoimmunity. *J Allergy Clin Immunol*. 2013;132:969-971.e2.
41. Wada T, Toma T, Okamoto H, et al. Oligoclonal expansion of T lymphocytes with multiple second-site mutations leads to Omenn syndrome in a patient with RAG1-deficient severe combined immunodeficiency. *Blood*. 2005;106:2099-2101.
42. Reiff A, Bassuk AG, Church JA, et al. Exome sequencing reveals RAG1 mutations in a child with autoimmunity and sterile chronic multifocal osteomyelitis evolving into disseminated granulomatous disease. *J Clin Immunol*. 2013;33:1289-1292.
43. De Ravin SS, Cowen EW, Zaremba KA, et al. Hypomorphic Rag mutations can cause destructive midline granulomatous disease. *Blood*. 2010;116:1263-1271.
44. Hirschhorn R. Overview of biochemical abnormalities and molecular genetics of adenosine deaminase deficiency. *Pediatr Res*. 1993;33:S35-41.
45. Sauer AV, Brígida I, Carriglio N, Aiuti A. Autoimmune dysregulation and purine metabolism in adenosine deaminase deficiency. *Front Immunol*. 2012;3:265.
46. Kessarwan C, Sokolic R, Cowen EW, et al. Multicentric dermatofibrosarcoma protuberans in patients with adenosine deaminase-deficient severe combined immune deficiency. *J Allergy Clin Immunol*. 2012;129:762-769.e1.
47. Hsu AP, Sampaio EP, Khan J, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood*. 2011;118:2653-2655.
48. Dickinson RE, Griffin H, Bigley V, et al. Exome sequencing identifies GATA-2 mutation as the cause of dendritic cell, monocyte, B and NK lymphoid deficiency. *Blood*. 2011;118:2656-2658.
49. Dickinson RE, Milne P, Jardine L, et al. The evolution of cellular deficiency in GATA2 mutation. *Blood*. 2014;123:863-874.
50. Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC syndrome in a patient with a GATA2 mutation: case report and review of the literature. *Clin Infect Dis*. 2013;57:697-699.
51. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nat Genet*. 2011;43:1012-1017.
52. Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nat Genet*. 2011;43:929-931.
53. Spinner MA, Sanchez LA, Hsu AP, et al. GATA2 deficiency: a protean disorder of hematopoiesis, lymphatics, and immunity. *Blood*. 2014;123:809-821.
54. West ES, Kingsbury MY, Mintz EM, et al. Generalized verrucosis in a patient with GATA2 deficiency. *Br J Dermatol*. 2014;170:1182-1186.
55. Mace EM, Hsu AP, Monaco-Shawver L, et al. Mutations in GATA2 cause human NK cell deficiency with specific loss of the CD56(bright) subset. *Blood*. 2013;121:2669-2677.
56. Poli A, Michel T, Thérésine M, Andrès E, Hentges F, Zimmer J. CD56^{bright} natural killer (NK) cells: an important NK cell subset. *Immunology*. 2009;126:458-465.
57. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, et al. Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. *Blood*. 2011;118:3715-3720.
58. Vinh DC, Patel SY, Uzel G, et al. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood*. 2010;115:1519-1529.
59. Pasquet M, Bellanné-Chantelot C, Tavitian S, et al. High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia. *Blood*. 2013;121:822-829.

60. Kreuter A, Hochdorfer B, Brockmeyer NH, et al. A human papillomavirus-associated disease with disseminated warts, depressed cell-mediated immunity, primary lymphedema, and anogenital dysplasia: WILD syndrome. *Arch Dermatol.* 2008;144:366-372.
61. Ostrow RS, Bender M, Niimura M, et al. Human papillomavirus DNA in cutaneous primary and metastasized squamous cell carcinomas from patients with epidermodysplasia verruciformis. *Proc Natl Acad Sci U S A.* 1982;79:1634-1638.
62. Zuelzer W. "Myelokathexis"—A new form of chronic granulocytopenia. Report of a case. *N Engl J Med.* 1964;270:699-704.
63. Hernandez PA, Gorlin RJ, Lukens JN, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet.* 2003;34:70-74.
64. Wetzler M, Talpaz M, Kleinerman ES, et al. A new familial immunodeficiency disorder characterized by severe neutropenia, a defective marrow release mechanism, and hypogammaglobulinemia. *Am J Med.* 1990;89:663-672.
65. Imashuku S, Miyagawa A, Chiyonobu T, et al. Epstein-Barr virus-associated T-lymphoproliferative disease with hemophagocytic syndrome, followed by fatal intestinal B lymphoma in a young adult female with WHIM syndrome. Warts, hypogammaglobulinemia, infections, and myelokathexis. *Ann Hematol.* 2002;81:470-473.
66. Chae KM, Ertle JO, Tharp MD. B-cell lymphoma in a patient with WHIM syndrome. *J Am Acad Dermatol.* 2001;44:124-128.
67. Beaussant Cohen S, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. *Orphanet J Rare Dis.* 2012;7:71.
68. Badolato R, Dotta L, Tassone L, et al. Tetralogy of Fallot is an uncommon manifestation of warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *J Pediatr.* 2012;161:763-765.
69. Mc Guire PJ, Cunningham-Rundles C, Ochs H, Diaz GA. Oligoclonality, impaired class switch and B-cell memory responses in WHIM syndrome. *Clin Immunol.* 2010;135:412-421.
70. Al Ustwani O, Kurzrock R, Wetzler M. Genetics on a WHIM. *Br J Haematol.* 2014;164:15-23.
71. Tassone L, Moratto D, Vermi W, et al. Defect of plasmacytoid dendritic cells in warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome patients. *Blood.* 2010;116:4870-4873.
72. McDermott DH, Liu Q, Ulrick J, et al. The CXCR4 antagonist plerixafor corrects panleukopenia in patients with WHIM syndrome. *Blood.* 2011;118:4957-4962.
73. Dale DC, Bolyard AA, Kelley ML, et al. The CXCR4 antagonist plerixafor is a potential therapy for myelokathexis, WHIM syndrome. *Blood.* 2011;118:4963-4966.
74. McDermott DH, Liu Q, Velez D, et al. A phase 1 clinical trial of long-term, low-dose treatment of WHIM syndrome with the CXCR4 antagonist plerixafor. *Blood.* 2014;123:2308-2316.

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Acute pain management in dermatology

Mechanisms and pathways

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Learning objectives

Define acute pain and distinguish acute pain from chronic pain; define the three categories of acute pain: preoperative pain, operative pain, and postoperative pain; delineate best practices for clinical assessment of the three categories of pain; and discuss the strengths and weaknesses of the visual analog scale as applied to acute pain in dermatology.

Disclosures

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The number of dermatologic surgical procedures performed is increasing each year. The pain associated with these procedures is a major concern for patients and its treatment is part of the increasing emphasis on outcomes and quality of clinical care. Better understanding of pain signaling and how commonly used analgesics function can help improve our surgical pain management. This is part I of a 2-part review that will highlight the anatomy of acute pain signaling from the skin to the central nervous system and the factors that influence the plasticity of the pathway. Having this foundation of knowledge is needed to enhance the clinical treatment of pain. Part II will provide an updated review of available treatments, with an emphasis on their appropriate use for postsurgical pain management. (*J Am Acad Dermatol* 2015;73:533-40.)

Key words: analgesic; anesthetic; chronic pain; hyperalgesia; pain; surgery; transduction.

INTRODUCTION

Key point

- As the number of dermatology surgical procedures increases, adequate perioperative pain control should be a goal of care

It is estimated that 75% of patients undergoing any surgery in the United States experience inadequate

pain control.¹ In response, national, state and local health care guidelines support perioperative pain control measures as a part of patient safety initiatives. As the number of dermatology procedures in the United States increases year after year,² dermatologists should be aware of the mechanisms of acute pain and the interventions to control patient's perioperative pain.

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Abbreviations used:

CNS:	central nervous system
COX:	cyclooxygenase
GABA:	gamma-aminobutyric acid
NSAID:	nonsteroidal antiinflammatory drug
PAG:	periaqueductal grey
RVM:	rostral ventromedial medulla
STT:	spinothalamic tract
TRP:	transient receptor potential

In part I of this continuing medical education article we review the anatomy and mechanisms of pain signaling from the skin to the central nervous system. We will break down the acute pain pathway into 4 main categories: cutaneous transduction, spinal cord processing, cortical perception, and descending regulation from the cortex. We will then discuss the plasticity of pain signaling via various regulatory factors and how they influence acute and chronic pain. This will allow better understanding for pain management, which will be discussed in Part II.

OVERVIEW OF ACUTE PAIN

Key points

- Pain sensation is evolutionarily advantageous, serving as a survival mechanism
- The pathway of acute pain can be divided into transduction, transmission, and perception

Evolutionarily, acute pain is a protective mechanism.³ It is a noxious sensation of short duration resulting from the sudden onset of traumatic injury, internal illness, or surgical procedure.⁴ Existentially, acute pain means “do that again at your own risk.” Pain sensation is the result of an exquisitely complex and dynamic peripheral and central neurologic system. The perception of pain is a subjective entity influenced by setting, past experiences, affect, sex, and cultural and cognitive factors.⁵ Disruption of the intricate balance of biologic and psychosocial aspects of pain can result in chronic pain.⁶ Acute pain and chronic pain are distinct, and a better understanding of their basic mechanisms can help guide more successful clinical treatment.

Pain can be simplified into 3 main processes: transduction, transmission, and perception. Transduction at the skin is the process of transferring a painful stimulus into electrical neuronal activity. Transmission through the spinal cord is the propagation of that electrical activity to the central nervous system (CNS). Perception within the brain is the final part of the pathway that leads to the subjective nature of pain that patients experience (Fig 1).⁷

CUTANEOUS TRANSDUCTION

Key points

- There are 3 main primary sensory afferent fibers: A β , A δ , and C
- Transducers are membrane receptors on primary afferents that are responsible for the sensation of sensory stimuli
- Nonneuronal skin cells have transducers and influence pain sensation
- Local anesthetics bind transducers to induce anesthesia

The skin is more densely innervated by, and contains more varied types of, sensory afferents compared to other bodily tissues.⁵ Cutaneous nerve fibers are highly specialized structures that work collectively with other tissues to transmit sensory information to the CNS.⁸ They have cell bodies in the dorsal root ganglion, peripheral terminals at target tissues, and central terminals in the spinal cord.⁶ This design allows rapid transmission from the periphery to the spinal cord.⁹

There are 3 broad categories of afferent sensory fibers: A β , A δ , and C fibers (Table 1).⁸ A β fibers respond to innocuous stimuli and detect texture, vibration, and light pressure.^{6,10} They are fast-conducting, large diameter, myelinated afferents that have nerve endings that often associate with nonneuronal cells (eg, Merkel cells, Pacinian corpuscles, and hair follicles) in their target tissues.^{6,11} A δ and C fibers respond to potentially injurious or noxious stimuli and are referred to as nociceptors.⁸ Nociceptors are free nerve endings because they do not directly associate with other cells or tissues at their peripheral terminals.¹¹ A δ fibers are medium diameter, lightly myelinated, and represent initial, sharp, localized pain.⁶ C fibers are small diameter, unmyelinated nociceptors that represent more diffuse, dull, aching pain.⁶

Transducers are membrane receptors on nociceptors that respond to specific stimuli (ie, thermal, mechanical, and/or chemical), allowing transduction of a stimulus into electrical activity. Transducers are either associated with a membrane ion channel (ionotropic receptors) or associated with a second messenger-signaling cascade (metabotropic receptors). Ionotropic receptors rapidly transmit sensory information because of their association with ion channels that generate action potentials. Metabotropic receptors are slower responders, but their second messengers can have profound effects on ionotropic receptor function.¹¹ Knowledge about transducer families, such as transient receptor potential channels (TRPs) and acid-sensing ion channels, has grown exponentially in recent years. There

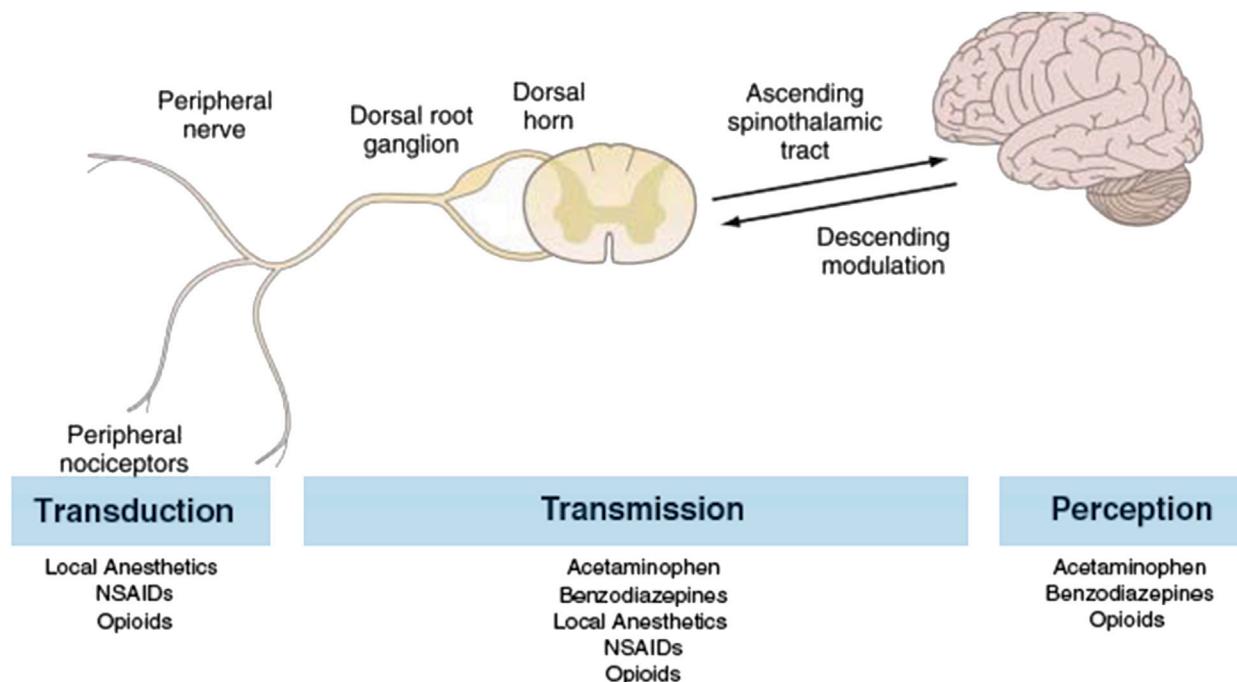


Fig 1. The pain pathway. Overview of the pain pathway and pharmacologic interventions that modulate signals at each point. Note that some pharmacologic interventions act at multiple points along the pain pathway. *NSAID*, Nonsteroidal antiinflammatory drug. (Adapted from Petersen EA, Whitworth LA. Pharmacologic treatment of pain. In: Winn HR, editor. Youmans neurological surgery, 6th ed. Philadelphia [PA]: Saunders; 2011. pp 1754-62.)

Table I. Characteristics of primary sensory afferents

	A β	A δ	C
Pain sensation	Vibration, pressure, and light touch	Sharp, pinprick pain	Dull, aching, burning pain
Diameter	Large	Medium	Small
Myelination	Heavy	Light	None
Time to induction of anesthesia	Slowest	Intermediate	Fastest

is extreme complexity and lack of specificity in transducers, which accounts for the polymodality (ability to respond to a variety of stimuli) of most sensory afferents.¹¹ A transducer may respond to multiple stimuli at different binding sites, such as TRPA1, which responds to both chemical and mechanical stimuli.⁶ Allosteric modification of a transducer can alter how it responds to its stimulus, such as the alteration in the TRPV1 response to thermal stimuli after binding extracellular protons.^{6,11} Much has been uncovered about transducer function and their interactions, but translation of this knowledge into clinically relevant therapeutic tools is still a goal of future research.

Although sensory transduction is primarily accomplished via neuronal afferents, recent evidence shows that nonneuronal cells express transducers.³ Keratinocytes and other epithelial cells have high transducer expression, providing a link

between the skin and neuronal afferents in pain signaling.⁶ Therefore, the transduction of sensory stimuli likely involves multiple cell types—neuronal and nonneuronal—along with a variety of receptors that interact to produce a pain sensation.⁵

Transduction of the sensory stimuli requires depolarization of the neuron's cell membrane and subsequent action potential generation.^{6,11} Local anesthetics, such as lidocaine, produce anesthesia by binding ionotropic receptors and preventing action potential generation.¹² Induction of anesthesia occurs at different rates depending on the nerve's thickness of myelination and the pH of the anesthetic solution. Lidocaine diffuses more quickly through the thinner myelination of pain-sensing C and A δ fibers and more slowly through the thicker myelination of pressure- and vibration-sensing A β fibers. Therefore, after local anesthetic injection a patient does not feel pain but does feel pressure at

Table II. Functions of spinal cord inhibitory interneurons

Interneuron function	Role	Type of pain prevented
Muting	Silences nociceptor firing in absence of noxious stimuli	Spontaneous
Attenuation	Allows appropriate response to noxious stimuli	Primary hyperalgesia
Limiting	Prevents spread of excitation to other spinal areas	Referred
Separating	Inhibit crosstalk between sensory modalities	Secondary hyperalgesia
Preventing	Block pathways that engrain pain memory	Chronic

the injection site.¹³ Local anesthetic onset is also determined by acidity of the anesthetic solution. Alkaline solutions have more nonionized molecules, which allows quicker induction of anesthesia because only the nonionized form can cross the nerve cell membrane and bind its intracellular receptor. The influence of pH on anesthetic onset is an important consideration when anesthetizing inflamed tissues, which create an acidic tissue environment.¹³ This is part of the reason that larger volumes of local anesthetic are needed to anesthetize inflamed areas, as seen in patients with inflammatory skin diseases, such as rosacea.

The addition of epinephrine to local anesthetics alters its clinical properties. Epinephrine causes local vasoconstriction, which decreases anesthetic vascular clearance, decreases the volume injected, decreases bleeding at the surgical site, and increases its duration of action.¹³ Epinephrine is only stable in acidic environments, which not only slows anesthetic onset, but also makes its injection painful. The addition of sodium bicarbonate to epinephrine/anesthetic solutions neutralizes the pH, reducing these limitations obstacles of epinephrine use.¹³

PROCESSING OF PAIN SIGNALS AT THE SPINAL CORD

Key points

- Sensory transmissions enter the dorsal horn of the spinal cord, where they interact with and are regulated by other neuronal components
- Interneurons, which make up the largest proportion of dorsal horn neurons, regulate pain transmissions
- The gate control theory uses interneurons to regulate pain transmissions
- Opiates act on ionotropic receptors in the spinal cord to induce analgesia

The spinal cord functions as a relay station for incoming neuronal transmissions.⁵ Four neuronal components interact at the dorsal horn of the spinal cord, primary afferent central terminals, spinal cord interneurons, projection neurons to higher cortical

areas, and descending axons from higher cortical areas.¹⁰ Inhibitory interneurons make up about one-third of all dorsal horn neurons and have several functions to regulate pain transmission (Table II).¹⁰ These regulatory functions result in control of local spinal signaling loops and determine what signals are transmitted to the cortex.¹⁴ Normal pain signaling requires proper function of inhibitory interneurons. When they fail to carry out their regulatory roles, pain signaling is altered and leads to the development of spontaneous pain, primary hyperalgesia, referred pain, secondary hyperalgesia, and chronic pain.^{10,14}

The gate control theory of pain, developed by Melzack and Wall in the 1960s, describes regulatory interneurons as “nerve gates,” which determine what signals are propagated to the cortex.¹⁵ A number of factors influence interneurons to either open or close a nerve gate, determining which pain transmissions are allowed to pass. For example, large A β fibers transmitting pressure and touch can override painful sensations transmitted by C and A δ fibers in the spinal cord, closing the gate on the nociceptors. This theory explains the postinjury relief felt by rubbing a knee after knocking it on a table.¹⁶ The same is true preinjury; a light pinch of the skin or use of vibration devices upon needle injection closes the gate on pain transmissions, providing pain relief.^{13,17}

Opiate receptors are abundant at the central terminals of primary afferents and at a lesser extent on the peripheral terminals.¹⁸ Upon agonist binding, these ionotropic receptors prevent the ion conductance necessary for the release of pain-signaling molecules.¹⁸ Therefore, via suppressing peripheral pain transmissions, opiates can provide analgesia when used during, or after, a procedure that evokes pain.

CORTICAL TRANSMISSION AND PERCEPTION

Key points

- Pain transmissions from the spinal cord travel in neuronal projection systems to higher cortical structures, where the perception of pain occurs

- **Cortical structures express gamma-aminobutyric acid and opiate receptors that produces analgesia upon agonist binding**

Pain transmissions from the spinal cord travel through projection systems to reach higher cortical structures. Two of these ascending pathways are the spinothalamic tract (STT) and the spinobulbar projections, which terminate in the thalamus and brainstem, respectively.^{16,19} The thalamus and brainstem then form networks with multiple cortical structures resulting in perception of the pain transmissions. The STT is responsible for information about the location, quality, and intensity of pain stimuli.²⁰ The spinobulbar projections are involved in autonomic responsiveness, alerting and escape responses, and descending modulation of pain sensation.²⁰ No single brain area is essential for pain perception; the activation of multiple structures results in its sensation.⁶ Brain imaging studies helped identify structures consistently involved in pain perception, including the somatosensory cortex, anterior cingulate cortex, and insular cortex.²¹ The somatosensory cortex is associated with sensory discriminative aspects of pain, while the anterior cingulate cortex and insular cortex are associated with emotional aspects of pain.⁶ Many other brain regions likely play a role in pain perception; however, fully elucidating their involvement requires additional research.

Gamma-aminobutyric acid (GABA) receptor agonists and opiates provide analgesia by altering the transmission and subsequent cortical perception of pain signals.^{22,23} GABA receptors are abundant at the dorsal horn of the spinal cord and higher cortical structures.²² At the spinal cord, binding of GABA receptor agonists, such as benzodiazepines, results in analgesia via an overall decrease in pain transmissions through ascending projections. Although not fully understood, GABA acting at higher order cortical structures likely results in its sedative properties.²² The analgesic properties of opiates, as described previously, occur by preventing spinal pain transmissions to cortical structures. It is important to note that their receptors are also located throughout higher cortical structures; however, the role of these cortical receptors in analgesia is not fully understood.²³

DESCENDING PAIN REGULATION FROM THE CORTEX

Key points

- **Neuronal projections from the cortex to the spinal cord, such as the periaqueductal gray and the rostral ventromedial medulla, modulate pain signaling**

- **The cortical influence on spinal pain transmissions is responsible for the effect emotion and cognition have on pain perception; benzodiazepines alter the effects that cortical influence has on pain perception**
- **Opiates alter the signaling from the periaqueductal gray and the rostral ventromedial medulla to induce analgesia**

The spinal cord processing of cutaneous transmissions is modulated by descending cortical projections.¹⁴ Two brainstem areas project these neurons, the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM).¹⁶ The PAG and RVM work in concert together to influence pain transmissions by either facilitation or inhibition of afferent signals.²⁴ They exert this modulation via action on the interneurons in the dorsal horn of the spinal cord.¹⁶

Both the PAG and the RVM receive input from higher cortical structures that influence their descending signals. This cortical influence explains the effect that emotion and cognition can have on nociceptor processing.²⁴ Brain imaging studies show that cortical structures involved in pain sensation are activated with the anticipation of pain.²¹ That is, without any physical pain stimulus, the perception of pain occurs. In addition, this activation likely alters how an impending noxious event is perceived.²¹ Attention and distraction also influence perception of painful stimuli. If a patient focuses on a painful stimulus it is likely perceived as being more intense. Conversely, if a patient is distracted from a painful stimulus it is likely perceived as being less intense.²⁴ Anxiolytics, such as benzodiazepines, are one pharmacologic option that can help reduce the effects of anxiety and anticipation on pain sensation.

Opiates also exert their analgesic effects via the PAG–RVM system.²¹ The PAG and the RVM express all the classic opioid receptors and their activation, via endogenous or exogenous opiates, produces analgesia.²⁴ Opiate receptor activation increases PAG–RVM inhibition on nociceptor transmissions in the dorsal horn, preventing pain transmission.¹⁸

SENSITIZATION OF PAIN SIGNALING

Key points

- **Enhanced pain sensation, called hyperalgesia, is a normal protective response after tissue injury and inflammation**
- **Inflammation resulting from injury is a major contributor to the development of hyperalgesia**
- **Nonsteroidal antiinflammatory drugs block the synthesis of inflammatory mediators responsible for hyperalgesia**

- **The use of anesthetics and analgesics perioperatively can help prevent the development of hyperalgesia**

The pain pathway responsible for sensation of noxious stimuli is anything but static. It possesses extreme plasticity, allowing alteration in how it responds to stimuli after tissue injury or inflammation.⁸ Enhanced pain sensation, called hyperalgesia, occurs after tissue injury and inflammation and is a normal response that facilitates recuperative behavior and healing.²⁴ However, if it becomes unregulated and persistent, it contributes to the development of chronic pain.⁷

Primary and secondary hyperalgesia occur because of altered pain signaling after tissue injury.⁶ Primary hyperalgesia results from a decrease in threshold and an increase in strength of a response to a stimulus.²⁵ This explains why a painful stimulus, such as a needle pinprick, is more painful at an inflamed area, such as an abscess, than at a non-inflamed area. Secondary hyperalgesia results from the inappropriate regulation of incoming sensory transmissions by spinal interneurons.¹⁴ This dysregulation causes innocuous stimuli at areas surrounding injured tissue to feel painful.^{6,7} This explains why a light touch of a cotton swab near injured tissue is perceived as painful.

After injury, surrounding tissues secrete a variety of substances into the local environment (Fig 2).⁷ These include neurotransmitters, peptides, prostaglandins, cytokines, chemokines, extracellular proteases, and protons. Nociceptors recognize each of these proinflammatory factors via cell surface receptors.⁷ The local interaction of nociceptors and the inflammatory factors increases the excitability, and therefore sensitivity, of nociceptors to mechanical and thermal stimuli, changing in the perception of pain.^{6,14}

Prostaglandins activate metabotropic receptors to enhance pain transduction through ionotropic receptors, resulting in hyperalgesia.²⁶ Nonsteroidal antiinflammatory drugs (NSAIDs) block the cyclooxygenase (COX) involved in their synthesis, which reduces the pain and hyperalgesia that occur secondary to inflammation.⁶ There are 2 isoforms of COX that nonselective NSAIDs target equally: COX-1 and COX-2. COX-1 is constitutively expressed in many tissues and provides the prostaglandins necessary for homeostasis.²⁶ COX-2 expression is inducible and is increased by inflammatory mediators. For this reason, COX-2 selective analgesics, such as celecoxib, were developed to optimize antiinflammatory action and decrease the side effects associated with COX-1 inhibition, such as

in the gastrointestinal tract.²⁶ NSAIDs are not able to cross the blood–brain barrier (BBB), so their effects are only apparent outside the CNS.²⁶ Acetaminophen, on the other hand, is able to cross the BBB and exerts its analgesic effects in the CNS. Acetaminophen is a weak inhibitor of COX-1 and COX-2, and it lacks antiinflammatory activity. Recent evidence shows that its inhibition of a third COX isoform, COX-3, may be responsible for its analgesic and antipyretic effects.²⁷ Even though acetaminophen is widely used for its analgesic properties, its exact target and mechanism of action is not fully understood.²⁸

The use of anesthetics and analgesics perioperatively can reduce the severity of postinjury hyperalgesia.²⁹ Local anesthetics block pain transmissions, preventing the enhanced signaling that occurs during tissue injury.²⁹ Opiate receptor expression increases in the setting of inflammation in both the periphery and CNS. Therefore, their analgesic effects are more dramatic in the setting of acute injury and inflammation.¹⁸ Hyperalgesia sets up an environment that can lead to chronic pain, and its prevention is an important goal for acute pain management.¹⁴

OVERVIEW OF CHRONIC PAIN

Key points

- **The etiologies and treatments of chronic pain are distinct from acute pain**
- **Chronic pain is defined as pain that persists after the initial tissue injury has healed**
- **Chronic pain develops from alterations at various levels of the pain pathway**
- **Patients with baseline chronic pain experience acute pain differently compared to patients without chronic pain**

The International Association for the Study of Pain defines chronic pain as “pain without apparent biologic value that has persisted beyond the normal tissue healing time usually taken to be 3 months.”³⁰ Chronic pain has many different clinical presentations, which has made quantifying its prevalence difficult, leading to the various studies that estimate it to be between 20% and 60%.^{31,32} The approach to chronic pain treatment is different than acute pain.³¹ Despite their underuse, NSAIDs and acetaminophen are efficacious in the treatment of chronic pain and should be a part of any chronic drug regimen.^{33,34} Opiates should only be added to, but not substituted for, nonopiate treatments after the combinations of nonopiate medications fail to control chronic pain.³³ A multimodal approach to chronic pain management is more efficacious; a combination of analgesics will provide more relief than any single analgesic.

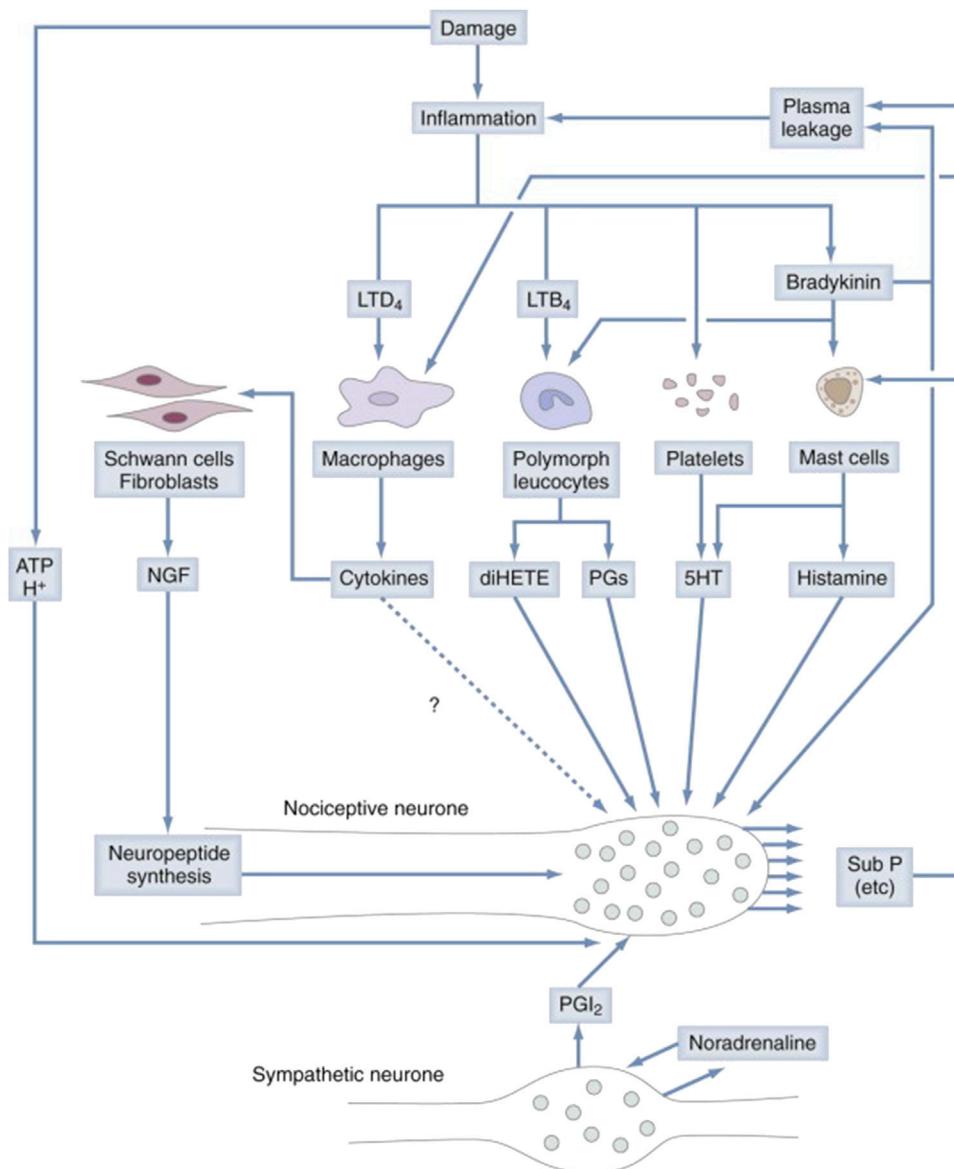


Fig 2. Peripheral inflammatory mediators. Overview of the factors and cells involved in the activation and sensitization of nociceptive neurons after tissue damage and inflammation. Note that substances released by inflammatory cells act on the nerve ending. Substances released by the nerve ending (eg, substance P) may in turn facilitate the inflammatory response. ATP, Adenosine triphosphate; diHETE, 8(R),15(S)-dihydroxyeicosatetraenoic acid; H⁺, protons; 5-HT, 5-hydroxytryptamine; LTB₄, leukotriene B4; LTD₄, leukotriene D4; NGF, nerve growth factor; PGI₂, prostacyclin; PGs, prostaglandins E1, E2, or F2 α . (Reprinted with permission from Baumann TK. Molecular basis of nociception. In: Winn HR, editor. Youmans neurological surgery, 6th ed. Philadelphia [PA]: Saunders; 2011. pp. 1740-8.)

Many modifications, such as the changes that occur in the setting of persistent hyperalgesia, account for the “transition” from acute to chronic pain. Second messenger systems alter the transduction of pain in primary afferent nociceptors.³⁵ Transmission of pain signals via ascending and descending neuronal projections is altered in chronic pain compared to acute pain states.²⁴ Cortical structures responsible for pain perception have increased

activation in chronic pain, which may account for the increased emotional and cognitive aspects of pain commonly seen in these patients.²¹

Acute pain is experienced differently in patients with chronic pain. Brain imaging shows that upon pain stimulation there is increased activation of pain-associated cortical regions compared to normal controls. The increase in the signal strength along the pain pathway contributes to the increased pain

sensation experienced by patients with chronic pain.²¹

In conclusion, acute pain begins as objective stimulus that triggers a transmissible electrochemical signal in a peripheral afferent and ends in the cortex, discerned and acted upon by several cortical areas. Understanding the processes and the cellular components that generate and transmit these signals helps clinicians design interventions. Acute postsurgical pain is borne before a needle or blade ever touches the skin. An individual can be primed for hyperalgesia, there are multiple biologic points in the peripheral and central nervous system that can be targeted to reduce pain, and preventing hyperalgesia can prevent complications, such as chronic pain. The treatment of acute and chronic pain is different. A successful treatment for one does not always apply for the other. Using a treatment ladder for pain management, as will be described in part II, will help guide analgesic therapy to obtain adequate pain control in patients with acute pain and patients with chronic pain.

REFERENCES

- Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003; 97:534-540.
- American Society for Dermatologic Surgery website. 2013 ASDS survey on dermatologic procedures. Available at: https://www.asds.net/_Media.aspx?id=7744. Accessed August 11, 2014.
- Tsunozaki M, Bautista DM. Mammalian somatosensory mechanotransduction. *Sens Syst*. 2009;19:362-369.
- Ball JW, Dains JE, Flynn JA, Solomon BS, Stewart RW. *Seidel's guide to physical examination*. 8th ed. Philadelphia (PA): Mosby; 2015.
- Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med*. 2010;16:1248-1257.
- Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell*. 2009;139:267-284.
- Bridgestock C, Rae CP. Anatomy, physiology and pharmacology of pain. *Anaesth Intensive Care Med*. 2013;14:480-483.
- Ringkamp M, Raja SN, Campbell JN, Meyer RA. Neurobiology of pain. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:1-30.
- Willis WD Jr. The somatosensory system, with emphasis on structures important for pain. *Brain Res Rev*. 2007;55:297-313.
- Todd AJ, Koerber HR. Neuroanatomical substrates of spinal nociception. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:77-93.
- Gold MS. Molecular biology of sensory transduction. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:31-47.
- Kankel J, Obreja O, Kleggetveit IP, et al. Differential effects of low dose lidocaine on C-fiber classes in humans. *J Pain*. 2012; 13:1232-1241.
- Hruza GJ. Anesthesia. In: Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. Elsevier Limited; 2012:2343-2352.
- Sandkuhler J. Spinal cord plasticity and pain. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:94-110.
- Mendell LM. Constructing and deconstructing the gate theory of pain. *Pain*. 2014;155:210-216.
- Steeds CE. The anatomy and physiology of pain. *Surg Med Publ*. 2009;27:507-511.
- Mally P, Czyz C, Chan N, Wulc A. Vibration anesthesia for the reduction of pain with facial dermal filler injections. *Aesthetic Plast Surg*. 2014;38:413-418.
- Dickenson AH, Kieffer BL. Opioids: basic mechanisms. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:413-428.
- Dostrovsky JO, Craig AD. Ascending projection systems. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:182-197.
- Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE, Hurley RW. *Pain pathways. Practical management of pain*. 5th ed. Saint Louis (MO): Mosby; 2014: 87-98.
- Apkarian AV, Bushnell MC, Schweinhardt P. Representation of pain in the brain. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:111-128.
- Reves JG, Glass PSA, Lubarsky DA, McEvoy MD, Martinez-Ruiz R. Intravenous anesthetics. In: Miller RD, ed. *Miller's anesthesia*. 7th ed. Philadelphia (PA): Churchill Livingstone; 2010:719-768.
- Fukuda K. Opioids. In: Miller RD, ed. *Miller's anesthesia*. 7th ed. Philadelphia (PA): Churchill Livingstone; 2010:769-824.
- Heinricher MM, Fields HL. Central nervous system mechanisms of pain modulation. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:129-142.
- Reichling DB, Green PG, Levine JD. The fundamental unit of pain is the cell. *Brinn Rev Pain*. 2013;154(suppl 1):S2-S9.
- Zeilhofer HU, Brune K. Cyclooxygenase inhibitors: basic aspects. In: McMahon SB, Koltzenburg M, Tracey I, Turk D, eds. *Wall & Melzack's textbook of pain*. 6th ed. Philadelphia (PA): Saunders; 2013:444-454.
- Brenner GM, Stevens CW. *Drugs for pain, inflammation, and arthritic disorders. Pharmacology*. 4th ed. Philadelphia (PA): Saunders; 2013: 314-327.
- Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC. *Principles of pain management. Bradley's neurology in clinical practice*. 6th ed. Philadelphia (PA): Saunders; 2012: 783-803.
- Gottschalk A, Smith SS. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Physician*. 2001;63:1979-1985.
- Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain Suppl*. 1986;3:S1-S226.
- Stein C, Kopf A. Anesthesia and treatment of chronic pain. In: Miller RD, ed. *Miller's anesthesia*. 7th ed. Philadelphia (PA): Churchill Livingstone; 2010:1795-1818.
- Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287-333.
- Munir MA, Enany N, Zhang JM. Nonopioid analgesics. *Pain Manag Part I*. 2007;91:97-111.
- Ferri FF, ed. *Pain management in chronic pain. Ferri's clinical advisor*. Saint Louis (MO): Mosby; 2015:872-874.
- Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends Neurosci*. 2009;32:6110-6118.

Acute pain management in dermatology

Risk assessment and treatment

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Learning objectives

Identify best evidence-supported practices for minimizing preoperative pain, operative pain, and postoperative pain.

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Dermatologists perform many procedures that require acute pain control with local anesthesia and, in some cases, management of postoperative pain. Identifying early risk factors before a procedure can better prepare both the patient and provider anticipate acute postsurgical pain needs. Taking a multimodal, algorithmic approach to managing acute postsurgical pain in dermatology practice can effectively attenuate acute postsurgical pain and reduce patient opioid requirements. (J Am Acad Dermatol 2015;73:543-60.)

Key words: acute postsurgical pain; cosmetic surgery; hyperalgesia; Mohs micrographic surgery; multimodal analgesia; nonsteroidal antiinflammatory drugs; opioids; preventive analgesia; skin cancer surgery.

INTRODUCTION

As described in part I of this continuing medical education article, acute pain is triggered by nociceptive, inflammatory, or neuropathic stimuli of peripheral nerve fibers and resolves within an appropriate healing period. How we perceive the intensity of and tolerate acute pain is affected by more than just the inciting trauma. Acute postsurgical pain (APSP) is

modulated by external and intrinsic physiologic factors: (1) intraoperative technique that stimulates nociceptive fibers; (2) postoperative cellular inflammatory signaling and downstream neuromodulation of afferent and cortical networks; and (3) preexisting neurologic and psychosocial factors that shape cortical centers that modulate the pain experience. In practical terms, these factors determine whether

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we experience transient hyperalgesia or intensification of hyperalgesia and chronic pain.

APSP remains a leading concern for patients, many of whom already have preexisting pain issues, pain experiences, or noncurated knowledge.^{1,2} When APSP is disregarded or provider interventions are inappropriately applied, patients are at greater risk for poor satisfaction and complications, including inferior wound healing, bleeding, insomnia, cardiovascular sequelae, transition to chronic pain, substance abuse, future exaggerated hyperalgesia, and psychological disorders.^{3,4} Managing APSP is integral to a cost effective, modern clinical practice. It is such a challenge in modern medical practice that adequate APSP management is considered a basic patient right codified into many US states' legal statutes and integrated into the standards of national regulatory bodies, such as the US Joint Commission, and the ethical framework of many medical societies and medical centers.^{5,6}

Acute postsurgical pain and dermatology procedures

Dermatology has become a procedure-intensive specialty. Between 1995 and 2008, the number of dermatology procedures performed in the United States more than doubled from 14 million to 30 million, the majority of which involved destruction of tissue and biopsy specimens obtained by dermatologists. In addition, the number of annual procedures the average dermatologist performed increased 60% to 1795.⁷ The epidemiologic data are weak, but APSP tends to be an infrequently reported complication in procedural dermatology. In one of the few dermatology studies to examine pain as a primary endpoint, Limthongkul et al⁸ reported that the majority of healthy patients who had undergone Mohs micrographic surgery (MMS) experienced mild to moderate postprocedure pain. Firoz et al⁹ noted that just more than half of patients who had undergone MMS in their cohort of 433 healthy patients required any pain medication and most of these were controlled with acetaminophen. Though follow-up was limited, these studies agree that the highest pain scores tended to be in the first few days, peaking on the day of surgery.

Aside from locoregional anesthesia and postoperative acetaminophen, there is little consensus on or even specialty-specific data to support how dermatologists should address APSP, in particular moderate to severe APSP. On one extreme, one provider may not give narcotics unless they are requested by the patient.⁹ On the other extreme, patients are given prescriptions for opioids, but most have pills left over after the perioperative period and, importantly, plan

to keep them for future use.¹⁰ This implies that dermatologists do not anticipate or predict postoperative pain severity well.

Multimodal analgesia is the use of ≥ 2 pharmacologic or nonpharmacologic interventions to attenuate hyperalgesia. The objective of this continuing medical education article is to provide evidence-based tools for an algorithmic and multimodal analgesia approach to anticipate and mitigate APSP and reduce narcotic requirements in patients undergoing dermatologic procedures.

PREOPERATIVE PAIN MANAGEMENT

Key points

- Screen to identify high-risk patients
- Pain catastrophization, multiple same-day procedures, and younger age confer a higher risk for acute postsurgical pain
- Patient education of acute postsurgical pain expectations and management may be beneficial
- Develop pain monitoring scale for periodic assessments baseline and after surgery

Identification of risks before surgery

Most dermatology procedures are of short duration and minimally invasive. Therefore, they confer low risk. Others are more extensive, such as excisions, skin grafting, resurfacing, and intuitively suggest a higher risk for APSP. However, the paucity of studies primarily evaluating these factors and contradictory results limit evidence-based risk stratification of patients. Limthongkul et al⁸ and Firoz et al⁹ concur that multiple same-day procedures and younger age are associated with greater APSP. However, other factors, such as surgery site, size of defect, amount of wound tension, and type of closure are not as clearly associated with APSP. For example, while Limthongkul et al⁸ identified the scalp as being significantly associated with higher APSP scores than periorbital, perioral, temple, neck, trunk, and extremity sites, Firoz et al⁹ found no difference in APSP risk comparing the head and neck to the trunk and extremities. In addition, while Firoz et al⁹ found that flaps and grafts were associated with greater APSP, Limthongkul et al⁸ did not. However, from other disciplines, extracutaneous factors have been shown to contribute to a patient's previous APSP experience, regardless of the procedure. Demographically, females and younger patients (especially those <31 years of age) are at greater risk for APSP. Obesity, a history of or a tendency towards pain catastrophizing, a history of depression, regular opioid or anxiolytic use, or a history of an underlying hyperalgesia syndrome

Table I. Risk stratification for minor procedures

Higher risk likely	Uncertain risk
History of hyperalgesia	Anatomic site
History of pain catastrophizing	Anxiety disorder or depression
Multiple same-day procedures	Body mass index
Patient age <31 years	Sex
Regular opioid or anxiolytic use	Size of defect
	Type of closure: linear repair, flap, or graft
	Tension on wound edge

(eg, fibromyalgia or complex regional pain syndrome) predict postsurgical hyperalgesia severity.¹¹⁻¹⁶ Providers or ancillary staff can rapidly assess risk factors for severe APSP during preoperative encounters to better identify patients who are at risk (Table I). However, more studies need to be conducted to more accurately risk-stratify patients undergoing dermatology procedures.

Pain assessment scale for monitoring

There are 4 commonly used, validated scales for APSP (Fig 1). The major drawback to these scales is that there is significant variation both between patients and at different time points for the same individual.¹⁷ The Wong Baker Faces pain scale is a recognized and validated tool for assessing APSP in children ≥ 3 years of age and adults.¹⁸⁻²¹ The Numeric Pain Intensity Scale (also known as the numerical rating scale [NRS]) is validated for adults and is arguably the easiest to integrate, because it is easy to administer either in person or over the phone. This scale assigns a numeric value for pain severity from 1 to 10, with 10 being most severe. The visual analogue scale (VAS) requires patients to place a mark between 2 endpoints on a line, which represents the spectrum of pain from no pain to severe pain and is assigned a value from 0 to 100. Generally, there is considerable concordance between VAS and NRS scales. A categorical rating scale (CRS) uses categories of pain (ie, none, mild, moderate, and severe) and can be administered over the phone or in person to adults. However, it has been shown to be less statistically sensitive to changes in pain compared to the VAS or NRS.¹⁷ Although the most commonly used pain assessment tools each have their drawbacks, choosing one to consistently use for your patients can still aid in risk stratification. It is critical to assess pain both before and after the intervention to identify efficacy. While it is important to assess APSP severity at rest, evaluating APSP on activity is more critical. Controlling this dynamic pain will have a greater impact on promoting

postprocedure mobilization and, therefore, prevent many complications.²² Selecting a validated pain scale that is appropriate for the patient, works within the clinic's capabilities, and satisfies the provider's objectives (eg, the Wong Baker Faces pain scale and the NRS) are critical in monitoring pain and selecting the appropriate intervention both during and after a procedure.

Patient education

Preoperative education about pain physiology and patient-directed pain management strategies may be helpful modulating cortical responses to and mitigating pain for high-risk patients.^{23,24} For example, Fincher et al²⁵ reported significant improvement in pain scores among children who were given preoperative education about a procedure and equipment used. However, patient-centered preoperative education interventions specifically targeting APSP show inconsistent results, although preoperative education does improve patient knowledge and attitudes towards APSP.^{26,27} In so far as to improve patient knowledge and attitudes, the method of information delivery is also important to the retention of information that may be beneficial in the postoperative period. In general, there is greater retention of preoperative information when delivered by multi-media content forms, such as videos or audio-augmented slides, over written methods, which are themselves superior to verbal instructions.²⁸⁻³⁰

OPERATIVE PAIN MANAGEMENT

Key points

- Regional blocks are better at reducing postoperative pain and reducing systemic toxicity risks of local anesthetics
- Anesthetic injection pain can be further reduced with buffered lidocaine or vibration
- Adjuvant anxiolytics reduce perioperative anxiety, but require additional safety monitoring
- Perioperative nonsteroidal antiinflammatory drugs or gabapentin reduces pain and opioid needs in the first 24 hours postprocedure

Locoregional anesthesia

The use of locoregional anesthetics has revolutionized procedural dermatology since the introduction of cocaine in 1884.³¹ Locoregional anesthetics allow for the elimination of local pain during a mucocutaneous procedure while allowing the patient to remain conscious and mobile for a rapid recovery. It has obvious safety advantages over general sedation, including greatly reduced morbidity and mortality risks, decreased respiratory

Numerical Rating Scale



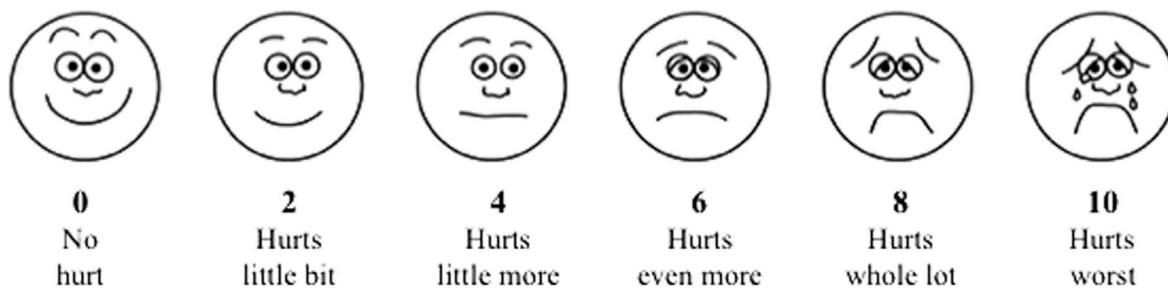
Categorical Rating Scale

Mild

Moderate

Severe

Wong-Baker FACES scale



Visual Analogue Scale (10cm long line)

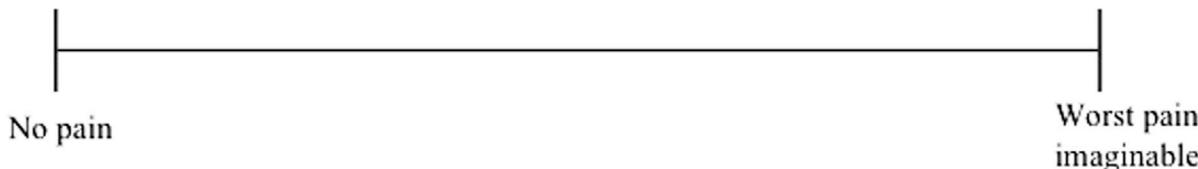


Fig 1. Summary of pain scales. (Wong-Baker FACES® Pain Rating Scale courtesy of the Wong-Baker FACES Foundation (2015). Retrieved with permission from <http://www.WongBakerFaces.org>.)

monitoring and nursing support requirements, rapid onset, and retaining cooperation of the patient.

Locoregional anesthetic agents, such as lidocaine, prevent the transduction of pain signals, the initial step in pain signaling. Locoregional anesthetic agents are divided into 2 classes (aminoesters and aminoamides) based on the covalent bonds that connect the hydrophobic and hydrophilic components of the molecules. Most are fast acting with short half-lives but some, such as ropivacaine, have analgesic effects that last for ≤ 24 hours (Table II). A relatively new formulation of liposomal bupivacaine has a long half-life of 72 hours compared to 24 hours for bupivacaine.³² This has shown some efficacy in general surgery as a postsurgical analgesic, reducing postsurgical pain, opioid use, and hospitalization costs; however, liposomal bupivacaine is ≥ 10 times more expensive compared to bupivacaine, and therefore its cost effectiveness in outpatient dermatology settings may be limited.^{33,34}

Choosing the right locoregional anesthetic is based on the objective of the anesthesia. In other words, do you need a fast-acting anesthetic that has a short half-life for a procedure that is otherwise not too painful, or prolonged analgesia after a procedure that is invasive or large or for a high-risk patient? For example, procedures with an obvious low risk for APSP, such as obtaining a shave biopsy specimen, may be better served with an anesthetic with a short half-life, such as lidocaine. In contrast, a 5-cm excision in a patient with a history of pain catastrophizing may be better served with an anesthetic with a long half-life, such as bupivacaine.

However, a patient's comorbidities and concomitant medications will also direct anesthetic choice. For example, bupivacaine and etidocaine should be used cautiously in patients with high-risk cardiac disease or taking medications, such as beta-adrenergic blockers, digitalis preparations, calcium

Table II. Summary of commonly used injected anesthetics

Injectable anesthetic	Onset, min	Without epinephrine		With epinephrine		Precautions
		Duration	Maximum	Duration	Maximum	
Bupivacaine 0.25% or 0.5%	5	2-4 hrs	>12 years of age, 175 mg	3-7 hrs	>12 years of age, 225 mg	Cardiotoxic effects at lower blood concentrations; pregnancy category C; avoid epinephrine in neonates
Lidocaine 1% or 2%	<2	30-60 min	Adults: 300 mg or 4.5 mg/kg; peds: 3.0 mg/kg	2-6 hrs	Adults: 500 mg or 7.0 mg/kg; peds: 5.0 mg/kg	Pregnancy category B; avoid epinephrine in neonates
Liposomal bupivacaine 1.3%	2-5	≤96 hrs	Adults: 266 mg			Cardiotoxic effects at lower blood concentrations; pregnancy category C
Mepivacaine 2% or 3%	3-5	45-90 min	Adults: 400 mg; peds: 5-6 mg/kg	2-6 hrs	Adults: 400 mg; peds: (lbs/150) × 400 mg	Pregnancy category C; avoid epinephrine in neonates
Prilocaine 4%	5	30-90 min	Adults: 5 mg/kg	3 hrs	<10 years of age: 6.6-8.8 mg/kg; 7 mg/kg	Associated with methemoglobinemia; pregnancy category B
Procaine 0.25%, 0.5%, or 1%	2-5	<60 min	Adults: 600 mg; peds: 15 mg/kg			Pregnancy category C
Ropivacaine 0.2%, 0.5%	1-5	2-6 hrs	Adults: 3 mg/kg	2-6 hrs	Adults: 3 mg/kg	Cardiotoxic effects at lower blood concentrations; pregnancy category B

Pregnancy category excludes epinephrine, which is category C.

Peds, Pediatric patients.

Adapted from the New York School of Regional Anesthesia website. Available at: <http://www.nysora.com/regional-anesthesia/foundations-of-ra/3492-local-anesthetics-clinical-pharmacology-and-rational-selection.html>. Accessed July 5, 2015.

channel blockers, and phenylephrine. These have a higher affinity for cardiac sodium channels than lidocaine and levobupivacaine, resulting in a greater risk for cardiac arrhythmias and subsequent hypotension. The use of less cardiotoxic anesthetics, such as lidocaine or mepivacaine, with a short onset time and intermediate duration, or regional nerve blocks should be considered in these patients.^{35,36} Patients with liver disease also need extra consideration when choosing an anesthetic. Metabolism of both esters and amides occurs, at least in part, in the liver via the P450 monooxygenase or Cytochrome p450 enzyme system. Therefore, their metabolism is affected by liver disease or other medications, such as cimetidine, that may reduce blood flow to the liver and predispose to liver toxicity.³⁷ In addition, metabolism of both esters and amides are affected by liver disease, pseudocholinesterase deficiency, and some prescription or herbal medications, such as midazolam, ginseng, and gingko. Therefore, dosing of local field therapy should be reduced by ≤50% to minimize the risk of toxicity or consider an alternative method, such as a nerve block, to reduce the amount used or tumescent anesthesia to dilute the anesthetic.

Aside from appropriately screening patients for contraindications, such as liver disease and extreme

age, and calculating appropriate weight-based dosing, providers should be aware of acute toxicity. Systemic toxicity starts with paresthesia of the tongue and lips and progresses to metallic taste, tinnitus, agitation, fasciculation, seizures, respiratory arrest and, if plasma concentrations are high enough, cardiac arrhythmias, such as prolonged PR interval, widening QRS and supraventricular tachycardia, and severe cardiovascular collapse. Toxicity may be seen as early as 5 minutes, but can be seen as long as 30 minutes after infiltration. Regional anesthesia (RA) carries the additional risk of traumatic nerve damage. The concomitant use of benzodiazepines has been recommended to prevent seizure risks associated with toxicity. However, benzodiazepines may obscure early and less catastrophic warnings of local anesthetic systemic toxicity.³⁸

Multiple administration techniques are available, including percutaneous, infiltrative, and regional anesthesia. By taking advantage of administration options and the unique properties (ie, time to onset, duration, and toxicities) of the multiple agents available, anesthetics can be tailored to individual patient and surgical needs.

Percutaneous anesthesia is the topical application of an anesthetic agent by way of iontophoresis or application of spray for mucous membranes or

creams/ointments for cutaneous sites. It is most appropriate for use in anticipated superficial procedures involving small areas to mitigate the pain of infiltrative anesthesia.³⁹

Infiltrative anesthesia is the injection of anesthetic agent into a mucocutaneous surgical site and the most commonly used method in dermatology. The field block is most commonly used for obtaining biopsy specimens, excisions, curettage and electro-dessication, and small flaps and grafts. It can be administered directly under a lesion, but for large areas or when a surgical site needs to be minimally disturbed, such as removing a cyst, a ring block can be administered with a “fan” technique around a site.

Tumescent anesthesia is a variant of infiltrative anesthesia that uses large volumes of diluted anesthetic agent for use in large surgical fields and for patients with comorbidities, such as liver disease or cardiomyopathy.⁴⁰ Multiple formulas are used, most commonly with lidocaine 0.05% to 0.1% with epinephrine diluted in 0.9% normal saline or Lactated Ringers; bupivacaine 0.5% has also been used. If using lidocaine, 35 mg/kg dosing is considered safe, but some have used doses as high as 55 mg/kg.⁴¹ Although popularly associated with liposuction, tumescent anesthesia has potential use for large flaps and other procedures, such as intra-lesional bleomycin, sclerotherapy, and large excisions.⁴²⁻⁴⁶ Tumescent anesthesia has the advantage of reducing the potential for systemic toxicity because less anesthetic may be used and, because plasma levels peak 10 to 14 hours after infiltration, patients may experience longer acute pain control than a ring block.⁴⁷ However, given the volumes injected, the slow rate of infiltration, and the dilution, procedures may be prolonged. Moreover, highly vascular areas, such as the head and neck, may absorb the lidocaine faster, resulting in peak plasma levels ≤ 6 hours.⁴⁸ Consequently, using the recommended 35 mg/kg dose and appropriately monitoring patients during and within 24 hours after a procedure are recommended, especially if using higher dosing and working on highly vascular areas.

Regional anesthesia is the injection of small volumes around selective nerves for the regional elimination of pain. Consequently, large surface areas can be anesthetized using smaller total anesthetic volumes, which also lead to less tissue distortion in the surgical field and targeting specific, sensitive anatomic areas. Moreover, studies in the orthopedic literature suggest that regional blocks, especially in the limbs, can provide better APSP analgesia than systemic analgesia.^{49,50} In animal models, regional nerve blocks also reduce acute inflammatory markers associated with central

sensitization and reduce the risk for hyperalgesia.^{51,52} Nerve blocks are appropriate for targeting specific anatomic locations, such as the nasal tip, the upper lip, and digits, et cetera, or for broader coverage of the entire hand or foot.

Local anesthesia pain reduction

Local anesthesia, however, causes acute pain in and of itself because of the needle and the anesthetic properties, such as its pH and pKa. This can contribute to patient anxiety and exacerbate acute pain both during and after surgery. Interventions made at the time of injection that take advantage of $A\beta$ fibers signal dominance in the dorsal horn can significantly reduce intensity of pain-related C fiber signals associated with local anesthesia administration.

The best evidence for a single intervention is for the use of so-called “buffered lidocaine,” a preparation consisting of sodium bicarbonate 8.4% and lidocaine 1% or 2% with epinephrine in a 1:10 ratio. A Cochrane metaanalysis has shown significantly better pain outcomes with buffered lidocaine compared to plain lidocaine infiltration for a variety of minimally invasive procedures. However, buffered lidocaine must be used within 1 week.⁵³ Zeiac et al⁵⁴ reported that a diluted mixture of lidocaine 1% with epinephrine in bacteriostatic sodium chloride 0.9% in a 1:10 ratio is also effective in managing pain with infiltrative anesthesia.

Although there are less robust data for their effectiveness, other interventions may decrease pain associated with injection include warming the lidocaine to body temperature (eg, rolling the filled syringe in the palms), counterirritation through pinching or vibration, or skin cooling. The use of vibratory stimulation devices, for example, has been reported in small series to decrease injection pain or to augment pain relief during minor procedures with minimal side effects, such as bruising.^{55,56} Several techniques have been reported, including applying a device at or near the injection site before injecting or applying the device in a circular motion to nearby tissue and simultaneous injection (Fig 2). Preinjection cooling using ice or cold saline bags (4°C) for 1 to 5 minutes has also been shown to be an individually effective method of reducing injection discomfort to the skin and mucosa.⁵⁷⁻⁶⁰ Individually, each technique can be used to improve the patient's local injection experience.

Needle size and technique are also contributory to minimizing injection pain. Needle size in the gauges used for most dermatologic procedures (ie, 27-31 G) likely tend to decrease the injection pain associated with intradermal injections. Another method is to

- A**
1. Demonstrate the sensation on another body part, such as the hand or finger.
 2. Contact the soft tissue and maintain light to moderate pressure for 5 seconds
 3. Inject the anesthetic into the soft tissue using a standard anesthetic technique.
 4. Continue to apply vibratory stimulation to the site for 5 seconds after withdrawal of the needle.

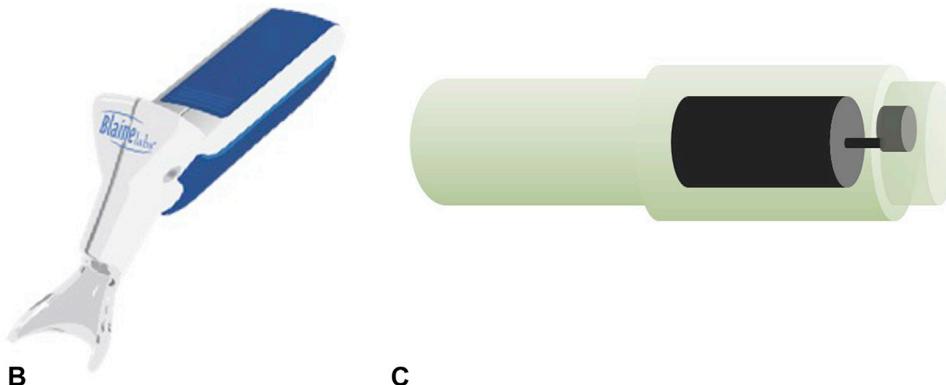


Fig 2. A sample technique on how to use a vibratory device (**A**) and examples of devices, including Blaine Labs' Vibration Anesthesia Device (Santa Fe Springs, CA) (**B**) and an illustration of an AA battery device that is available from several manufacturers (**C**).

pause after an initial subdermal injection with a small aliquot before injecting slowly (eg, over 30 seconds) larger volumes and reinserting the needle within 1 cm of blanched areas.⁶¹

Data suggest that psychological interventions can be used to reduce APSP in certain patient populations. For example, hypnosis or distraction techniques, such as watching videos, listening to music, or talking, reduce pain experiences, especially for children and adolescents.⁶²⁻⁶⁵ Newborns benefit from swaddling or sucking-related interventions, but there is no consistent data showing an effective psychological intervention for older infants.⁶⁶

Perioperative anxiolytics

Benzodiazepines are excellent amnestic and anxiolytics that may be administered intranasally, orally, or intravenously (Table III). Benzodiazepines, such as midazolam and alprazolam, enhance the effects of the GABA_A receptor at the level of the cortex and spinal cord, increasing the overall conductance of these inhibitory channels. Among healthy adults undergoing MMS, Ravitskiy et al⁶⁷ found that in a placebo-controlled, double-blind study orally administered midazolam 10 mg significantly reduced patient perioperative anxiety and

blood pressure with no clinically significant adverse effects. Otley et al⁶⁸ found similar results when oral midazolam was given to a prospective series of pediatric patients undergoing dermatologic surgery. However, adverse effects include, most notably, drowsiness and respiratory depression, which require commitment of nursing resources to intra- and postoperative patient monitoring for ≤ 1 hour after the procedure, and may impact postsurgical mobility and independence. In <1% of patients administered a benzodiazepine, a paradoxical reaction may cause agitation, restlessness, hyperactivity, and combativeness, which requires intravenous infusion of flumazenil.⁶⁹ Therefore, although perioperative anxiolytics can be helpful in high-risk APSP patients and the pediatric population, their use may be limited by adverse side effects and the extra staff they required for patient monitoring.

Preventive analgesia

Preventive analgesia techniques, such as single-dose medication administered before, during, or immediately after a procedure have some efficacy in reducing intra- and postoperative pain ≤ 24 hours after a procedure, reduce opioid use, and prevent hyperalgesia syndromes.⁷⁰ For example, single-dose

Table III. Summary of benzodiazepines

Benzodiazepine	Onset	Duration	Adult dosage	Precautions
Alprazolam IR	PO: 1 hr	4-6 hrs	0.5 mg PO	Caution: elderly, obese, and advanced hepatic disease may increase duration to >15 hrs; contraindicated: narrow-angle glaucoma, concurrent use with ketoconazole or itraconazole
Chlordiazepoxide	PO: 0.5-2 hrs		10 mg PO	Caution: elderly, advanced hepatic disease, or renal disease (reduce 50% for CrCl <10 mL/min)
Clonazepam	PO: 20-40 min	<12 hrs	0.25 mg PO	Not indicated for perioperative use
Diazepam	PO: min; IV: immediate	IV: 20-30 min; PO: variable	2-10 mg PO or IV	Caution: neonates, elderly, and patients with severe hepatic dysfunction may experience duration of action of 50-100 hrs; contraindicated: myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, sleep apnea syndrome, or acute narrow-angle glaucoma
Lorazepam	PO: 30-60 min; IM: 20-30 min; IV: 2-3 min	8 hrs	1-2 mg PO; 0.05 mg/kg max of 4 mg IM; 2 mg IV	Contraindicated: acute narrow-angle glaucoma, sleep apnea (parenteral), intraarterial injection of parenteral formulation, or severe respiratory insufficiency
Midazolam	PO: 10-20 min; IM: 15 min; IV: 3-5 min	1-6 hrs	5-20 mg PO; 0.07-0.08 mg/kg IM; 1-2.5 mg IV over 2-3 min	Caution: elderly (reduce dose), chronic obstructive pulmonary disease (reduce dose), concomitant narcotic or other CNS depressants (reduce dose), congestive heart failure, or renal failure; contraindicated: narrow-angle glaucoma

Cross-sensitivity with other benzodiazepines may exist. IM administration is not recommended. Midazolam dose reduction to about 0.25 mg/kg PO. Pregnancy category D.

COX, Cyclooxygenase; CrCl, creatinine clearance; IM, intramuscular; IV, intravenous; IR, immediate release; PO, per os.

acetaminophen \leq 1 g, ibuprofen 400 mg, diclofenac 50 mg, or etoricoxib 120 mg dosing immediately after surgery reduces postoperative pain and opioid consumption.^{71,72} Comparing single-dose ibuprofen 400 mg to low-dose celecoxib 200 mg or celecoxib 400 mg after minor surgery, there is no difference in pain relief in the first hours, but pain relief lasts longer (24 vs. 9 hours) in patients who were treated with celecoxib.^{73,74} Therefore, preventive analgesia's use in the ambulatory surgical setting may be beneficial for APSP reduction and control for high-risk dermatologic procedures. The use of preemptive analgesia may be most effective when a multidose approach is used. For example, celecoxib 200 mg given every 12 hours starting the night before a face lift significantly reduced pain scores compared to a single dose of a nonsteroidal antiinflammatory drug (NSAID) before surgery, which has not shown a consistent reduction of APSP.^{75,76}

Although the use of other intraoperative adjuvants, such as gabapentinoids, benzodiazepines, or

glucocorticoids, for perioperative analgesia and antihyperalgesia have not been evaluated specifically in dermatology, other surgical specialties have found preventive adjuvants useful in mitigating severe APSP. For select patients, such as those higher-risk patients for chronic postsurgical pain, gabapentin and pregabalin can prevent hyperalgesia by inhibiting central sensitization via inhibition of alfa-2-delta subunits of calcium channels. Therefore, the use of gabapentinoids can significantly reduce postoperative pain and opioid consumption in the first 24 hours after major surgeries.⁷⁷ For example, when administered 1 to 2 hours before surgery in doses of 300 to 1200 mg, gabapentin has significant analgesic effect compared to placebo.⁷⁸ In addition, gabapentinoids may also reduce the risk of chronic postsurgical pain.⁷⁷ Glucocorticoids, such as intravenous dexamethasone, block cyclooxygenase (COX) and lipooxygenase enzymes and show significant but limited analgesic effects with no concomitant increased risk for wound infection or

nausea when administered perioperatively in general surgery, but its route and potential for complications, such as hyperglycemia, are likely prohibitive in dermatology.⁷⁹ While the anxiolytic effects of benzodiazepines are well known, limited data suggest that there are antihyperalgesia effects, possibly by targeting receptors in the spinal cord. However, randomized controlled trials of benzodiazepines in minor procedures have not shown clinically significant analgesic effects.⁸⁰⁻⁸²

POSTOPERATIVE PAIN MANAGEMENT

Key points

- Nonsteroidal antiinflammatory drugs are effective at postoperative pain control
- Nonsteroidal antiinflammatory drugs and acetaminophen reduce opioid requirements
- Opioids should be second-line therapy

The critical postoperative period is in the first few days after the procedure, when hyperalgesia is likely at its worst. In postoperative pain plans or after identifying a patient in a worsening pain state, providing appropriate and safe interventions is critical.

Cold analgesia

While pain and temperature are carried by C fibers, stimulating temperature receptors may override pain signals and edema and may significantly reduce APSP scores after mucocutaneous procedures. For example, small series have suggested that use of ice or gel cold packs at the site during or after surgery decreases pain and/or postoperative narcotic use in the first few days of the postoperative period.⁸³⁻⁸⁷ However, application varies from 10 to 20 minutes and for ≤ 72 hours after surgery. More research should be conducted on this low-cost, simple method to control APSP.

Acetaminophen

Acetaminophen remains the mainstay of pain management for minor dermatology procedures.⁹ Acetaminophen inhibits central nervous system prostaglandin synthesis and possibly the COX-3 pathway, but has weak effects on peripheral prostaglandin synthesis and inflammation.⁸⁸⁻⁹⁰ Acetaminophen in doses of 500 mg to 1g provides significant pain reduction for mild to moderate pain over 4 to 6 hours; significantly, this is not dose-dependent, and therefore lower doses are recommended.⁹¹ For low-risk procedures, then, a dose of 500 mg 3 times a day is likely sufficient for mild pain relief. Acetaminophen administered at 1 g by mouth every 6 to 8 hours has rare, significant side effects, such as

Stevens-Johnson syndrome and liver failure, in the usual dose range of ≤ 4 g per day (3 g per day in patients >60 years of age), but at higher doses does have a risk of hepatic toxicity. Acetaminophen is the preferred analgesic in patients with advanced liver disease, because of the risks of bleeding and hepatorenal syndrome. For these patients, their maximum daily dose is reduced to 2 g per day.^{92,93}

Nonsteroidal antiinflammatory drugs

NSAIDs, such as ketorolac, ibuprofen, naproxen, celecoxib, etoricoxib, and aspirin, are commonly recommended first-line therapies for the treatment of mild to moderate APSP. NSAIDs are capable of an approximately 50% reduction in postoperative pain and significantly reduce future opioid requirements (Table IV).^{13,89,94-98} Recall, from part I of this continuing medical education article, that NSAIDs reduce inflammation and nociceptive pain through selective or nonselective COX receptor inhibition at the level of the spinal cord and peripheral prostaglandin inhibition at the level of terminal axons. It is postulated that COX-2 inhibition is responsible for inflammation and pain reduction, while COX-1 inhibition is linked to the renal and gastric adverse events in at-risk patients.

Nonselective NSAIDs inhibit COX-1 and may impair renal perfusion, exacerbate preexisting renal dysfunction, and weaken the gastric mucosa's protective lining and lead to gastric perforation. While COX-2 inhibitors are associated with increased cardiovascular morbidity and some have been removed from the market, short courses of low-dose COX-2 inhibitors, such as celecoxib 200 mg, have been used safely.⁹⁹ In patients with a history of gastrointestinal ulcers, the risk of short-term use of NSAIDs is unknown but likely minimal. Existing data support recommendations that patients >65 years of age or with a history of peptic ulcer disease concomitantly be given gastroprotective agents, such as misoprostol 200 μ g 4 times daily or omeprazole 20 mg daily.¹⁰⁰⁻¹⁰³ Acute side effects are rare, but include Stevens-Johnson syndrome, nausea, vomiting, and tinnitus in healthy patients. NSAIDs may exacerbate underlying, treated conditions, such as liver disease, hypertension, and kidney disease, or induce life-threatening hepatorenal syndrome in patients with cirrhosis. In addition, NSAIDs interact with common medications, including anticoagulants, diuretics, angiotensin-converting enzyme inhibitors, glucocorticoids, and antineoplastic doses of methotrexate.¹⁰⁴

Aspirin, a salicylate, is a nonselective NSAID that is predominantly used for its cardioprotective effects

Table IV. Summary of nonsteroidal antiinflammatory drugs

NSAID	Type	Onset, min	Duration, hours	Adult dosage	Precautions
Celecoxib	Selective COX-2	30-60	8	400 mg PO	Contraindicated: advanced renal disease
Diclofenac	Nonselective	30-60	6-8	18-35 mg PO	Contraindicated: advanced renal disease; sulfa allergy
Etoricoxib	Selective COX-2	30	6-8	120 mg PO	Caution: mild to moderate liver disease (60 mg PO daily to 30 mg daily); contraindicated: advanced liver disease (Child-Pugh ≥ 10)
Ibuprofen	Nonselective	30-60	4-6	200-800 PO or IV	Caution: liver disease or peptic ulcer disease; contraindicated: advanced renal disease; other: IV infusion over 30 min
Indomethacin	Selective COX-1	30-60	4-6	20-40 mg PO	Contraindicated: advanced renal disease
Ketorlac	Nonselective	30	4-6	60 mg IM; 30 mg IV; 20 mg PO	Caution: elderly (reduce dose by 50%); contraindicated: advanced renal disease; max dose: 120 IV/IM or 40 mg PO
Naproxen	Nonselective	30-60	<12	500 mg PO	Contraindicated: advanced renal disease

NSAIDs increase the risk of serious gastrointestinal adverse events, including bleeding, ulcer, and stomach or intestine perforation, which can be fatal and may occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. NSAIDs are contraindicated in patients with advanced renal disease (estimated glomerular filtration rate, <30 mL/min). Class contraindications to use include hypersensitivity to other NSAIDs, history of asthma, urticaria, or allergic-type reaction to aspirin or other NSAIDs.

COX, Cyclooxygenase; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal antiinflammatory drug; PO, per os.

at low doses and is not commonly used for pain control because of its side effects and access to safer alternatives, such as ibuprofen. However, aspirin has been shown to be generally effective for ≤ 12 hours for the treatment of moderate to severe APSP at high single doses of 900 to 1200 mg immediately postoperatively, although the risks for drowsiness and gastrointestinal complications increased.¹⁰⁵ While the risk of analgesic dosing of aspirin for harm to cutaneous flaps and grafts has not been specifically examined, the risks for complications likely increases. Literature evaluating postoperative thromboprophylaxis with aspirin after microvascular free-tissue transfer suggests increased risks for hematomas and salvage rates.^{106,107} Acute toxicity can occur with aspirin doses > 150 mg/kg and can cause nausea, tinnitus, hyperthermia, hypoglycemia, seizure, and pulmonary edema. Its pervasive use as a cardioprotective antithrombotic deserves special mention. Despite evidence that aspirin prolongs bleeding time because of its irreversible binding to platelets for ≤ 14 days, the lack of evidence to support life-threatening bleeding as a result of continuing cardioprotective doses of aspirin and the growing evidence that stopping antithrombotic medications has been associated with life-threatening cardiovascular events has led to a growing consensus that continuing cardioprotective doses of aspirin therapy is tolerable during minor cutaneous procedures.¹⁰⁸⁻¹¹²

Of special note, the impairment of hemostasis and platelet aggregation caused by NSAIDs has led to concerns about perioperative bleeding complications and limited its adoption as a postoperative analgesic in dermatology surgery practice. Studies have found that both aspirin and other NSAIDs induce increased bleeding times—aspirin more significantly than ibuprofen, likely because of its irreversible binding to platelets. However, most elevated bleeding times in patients taking ibuprofen are within the laboratory normal range and, because binding to platelets is transient, lasts only hours.¹¹³⁻¹¹⁵ The clinical implications, however, for wound complications—such as hematomas, dehiscence, or bleeding—that are directly related to postoperative NSAID use are conflicting, likely representing disparities in research. Otorhinolaryngologists, however, have extensive experience with perioperative ibuprofen in tonsillectomies and show largely no significant risk for postoperative bleeding complications.¹¹⁶ The use of concurrent anticoagulation with low-dose aspirin and concomitant NSAIDs incurs a low risk for complications, such as dehiscence or hematoma, in the general literature.¹¹⁷⁻¹¹⁹ In a small case series, Lawrence et al¹¹³ found that intraoperative complications in cutaneous surgery arising from concurrent aspirin or NSAIDs were limited to bleeding caused by aspirin and postoperative bleeding could be attributed to neither medication. Therefore, for minor dermatologic procedures, such

as obtaining a biopsy specimen and small excisions, the use of NSAIDs in general likely confers a low risk for bleeding complications. However, there is a dearth of well-designed studies directly examining bleeding complications in complex procedures, such as flaps and grafts. Indirect evidence in marketing studies suggests that the postoperative use of ibuprofen does not confer greater bleeding complications to wounds compared to acetaminophen.¹²⁰ However, the use of ketorolac may be linked to bleeding complications and there may be different risks for adult and pediatric populations.^{121,122} The risk, if any, attributed to perioperative analgesic doses of aspirin or NSAIDs for large excisions, flaps, and grafts deserves future research given the potential efficacy NSAIDs in pain control.

Nonsteroidal antiinflammatory drugs compared to acetaminophen

Individually, metaanalyses show that for minor procedures, NSAIDs at a dosing of ibuprofen 200 to 400 mg are superior to acetaminophen 600 to 1000 mg for acute pain control when given in the first 6 hours postprocedure.¹²³ In addition, the combination of ibuprofen and acetaminophen may be safe and superior to either medication used alone immediately after minor procedures to manage moderate to severe acute pain in adults and children.¹²⁴⁻¹²⁶ In one of the few randomized control studies in the dermatology literature, Snizek et al⁹⁰ compared acetaminophen 1000 mg to the combination of acetaminophen 1000 mg and ibuprofen 400 mg given immediately postsurgery and every 4 hours for ≤ 4 doses after MMS. The cohort given the combination therapy had lower pain scores at all intervals, and significant differences reached until the third dose.⁹⁰ However, there is a limit to therapeutic efficacy of NSAIDs and acetaminophen, and some patients may require adjunct medications.

Opioids

Opioids target opioid receptors in the spinal cord and cortex. There are 4 classes of opioids, consisting of phenanthrenes, benzomorphans, phenylpiperidines, and diphenylheptanes, as well as atypical opioids. Class distinction is important when choosing an opioid for a patient with the rare true allergy, because an opioid from a different class can be selected in these situations. For example, a patient with an allergy to codeine from the phenanthrene class can be substituted with fentanyl from the phenylpiperidine class or tramadol. However, the majority of commonly prescribed outpatient opioids come from the phenanthrene class, and if

alternative opioids are not apparently available, then the high-risk patient should be referred to a pain management specialist for consultation before surgery.

Opioids have traditionally and reflexively been used and recommended for moderate to severe pain management, but in reality they are often used for mild to moderate pain, too.^{89,94} The analgesic effect can be rapid and effective in many cases, and dosing ranges are broad, limited only by side effects (Table V). Further complicating opioid use are the analgesic effects from opioids, which are extremely variable and patient-dependent—resulting in less efficacy than might be expected, given the reputation of opioids. Codeine is the least tolerated opiate and has been removed from many formulations for the following reasons: (1) metabolism to the active form (morphine) is inefficient, producing many side effect-inducing metabolites; (2) 10% of patients lack the enzyme to metabolize codeine and therefore get no analgesia (pain relief comes from the acetaminophen component only); and (3) 1% to 2% of patients are ultrarapid metabolizers, and may suffer severe opiate intoxication.¹²⁷ In 1 review of acute postoperative pain, oxycodone 5 mg was inferior in providing $\leq 50\%$ pain relief over 6 hours after surgery to ibuprofen 400 mg or ibuprofen 400 mg/oxycodone 5 mg.¹²⁸

Moreover, the class' adverse effect profile makes it a second-line therapy for postoperative pain control after minor procedures. All opiates possess common adverse effects that may require additional interventions, including nausea, constipation, and respiratory depression. Therefore, adjuvants to counter side effects, such as stool softeners and antiemetics, should be concomitantly given to patients who are prescribed opioids. Moreover, opioids have many drug interactions and contraindications, which restrict their use or should be used with utmost caution in many patients, especially elderly patients. More seriously, opioid use is associated with the paradoxical development of hyperalgesia, which can impact future pain medication dosing requirements and pain perception.^{129,130} Finally, regular opioid use for as little as 1 week can lead to dependence and the acute complications of withdrawal.¹³¹ For patients for whom tolerance has developed, such as patients concurrently taking an opioid, taking the opioid before and after the procedure and augmenting with additional analgesia is appropriate. Class switching or consultation with a pain specialist should be considered for patients with a high tolerance with or without dependency history or for whom a true allergy has developed.

Table V. Summary of opioids

Opioid	Class	Potency	Onset	Duration, hrs	Adult dosage	Precautions
Tramadol	Atypical opioid	Weak	PO: 1 hr	9	PO: 50-100 mg	Caution: renal disease (for CrCl <30 mL/min, administer 50-100 mg dose every 12 hrs and maximum 200 mg/day), liver disease (avoid extended release), and cirrhosis (dose 50 mg every 12 hrs)
Codeine	Phenanthrenes	Weak	PO: 30-60 min	4-6	PO: 15-60 mg	Caution: elderly (CNS depression, constipation), renal disease (CrCl 10-50 mL/min: administer at 75% of dose; CrCl <10 mL/min: administer at 50% of dose); liver disease (increases duration of action)
Oxycodone	Phenanthrenes	Strong	PO: 10-30 min	3-6	PO: 5-10 mg	Caution: renal disease (CrCl <60 mL/min) and liver disease (reduce dose by 50%)
Hydromorphone	Phenanthrenes	Strong	PO: 15-30 min; IV: 5 min	3-4	PO: 2-4 mg; IV: 0.2-1 mg	Caution: renal disease (CrCl <60 mL/min) and liver disease (reduce dose by 25-50%)
Fentanyl	Phenylpiperidines	Strong	IV: immediate; IM: 7-15 min; patch: 6 hrs	IV: 0.5-1; IM: 1-2; patch: 72	IV: 25-100 µg/dose; patch: 25-100 µg/hr	Caution: cardiac bradyarrhythmias, chronic obstructive pulmonary disease, patients with decreased respiratory reserve
Morphine	Phenanthrenes	Strong	PO: 30 min; IM/IV: 5-10 min	4	PO: 10-30 mg; IM: 5-10 mg; IV: 2.5-5 mg	Caution: renal disease (CrCl 10-50 mL/min: administer at 75% of dose; CrCl <10 mL/min: administer at 50% of dose); liver disease (increases duration of action)

For immediate release formulations only. Fentanyl transdermal patch are recommended for chronic, not acute pain.

CNS, Central nervous system; CrCl, creatinine clearance; PO, per os; IM, intramuscular; IV, intravenous.

Combination medications

Monotherapy is sometimes not adequate for pain relief; a la carte combinations of classes or patient-friendly, manufactured combinations, such as acetaminophen–oxycodone, ibuprofen–hydrocodone, acetaminophen–caffeine, or acetaminophen–codeine, are required for mild to moderate pain

control (Table VI). Combining acetaminophen and an NSAID, for example, shows significant analgesic effects for moderate to severe pain with minor and expected side effects related to each drug.¹²⁴ In addition, the combination of acetaminophen and ibuprofen showed superiority to acetaminophen 325 mg/codeine 30 mg after MMS.⁹⁰ Metaanalyses

Table VI. Summary of combination analgesics

Combination	Onset, min	Duration, hrs	Adult dosage
Codeine plus acetaminophen	PO: 30-60	4-6	Codeine: 15-60 mg; acetaminophen: 300-650 mg
Hydrocodone plus acetaminophen	PO: 10-60	4-8	Hydrocodone: 5-10 mg; acetaminophen: 325-750 mg
Hydrocodone plus ibuprofen	PO: 30	4-8	Hydrocodone: 5-10 mg; ibuprofen: 200 mg
Oxycodone plus acetaminophen	PO: 10-15	3-6	Oxycodone: 2.5-10 mg; acetaminophen: 300-325 mg
Oxycodone plus ibuprofen	PO: 10-30	3-6	Oxycodone: 5 mg; ibuprofen: 400 mg
Oxycodone plus aspirin	PO: 10-30	3-6	Oxycodone: 4.8 mg; aspirin: 3325 mg
Tramadol plus acetaminophen	PO: 30-60	6-9	Tramadol: 37.5 mg; acetaminophen: 325 mg

PO, Per os.

and reviews of manufactured combinations of traditional opioid–nonopioid analgesics for all types of surgery have postoperative pain relief for all types of surgeries.⁷² However, prescribers are limited both by the fixed dosing of manufactured combinations and the toxic limits and side effects of each component, usually the nonopioid. More research should be conducted examining the efficacy and risk of harm when combining new or nontraditional combinations, such as gabapentin and ibuprofen.¹³²

Adjuvant medications

Adjunctive medications target cortical structures and are typically used to treat common psychological pathology and cancer pain.⁹⁵ This approach should be considered in the management of chronic rather than acute pain. However, recent studies suggest that adjuvants, like fluoxetine, may have antiinflammatory and antihyperalgesic effects.¹³³ Additional studies are warranted to determine if there is an association of decreased postoperative pain management of patients that receive a therapeutic regimen of fluoxetine.

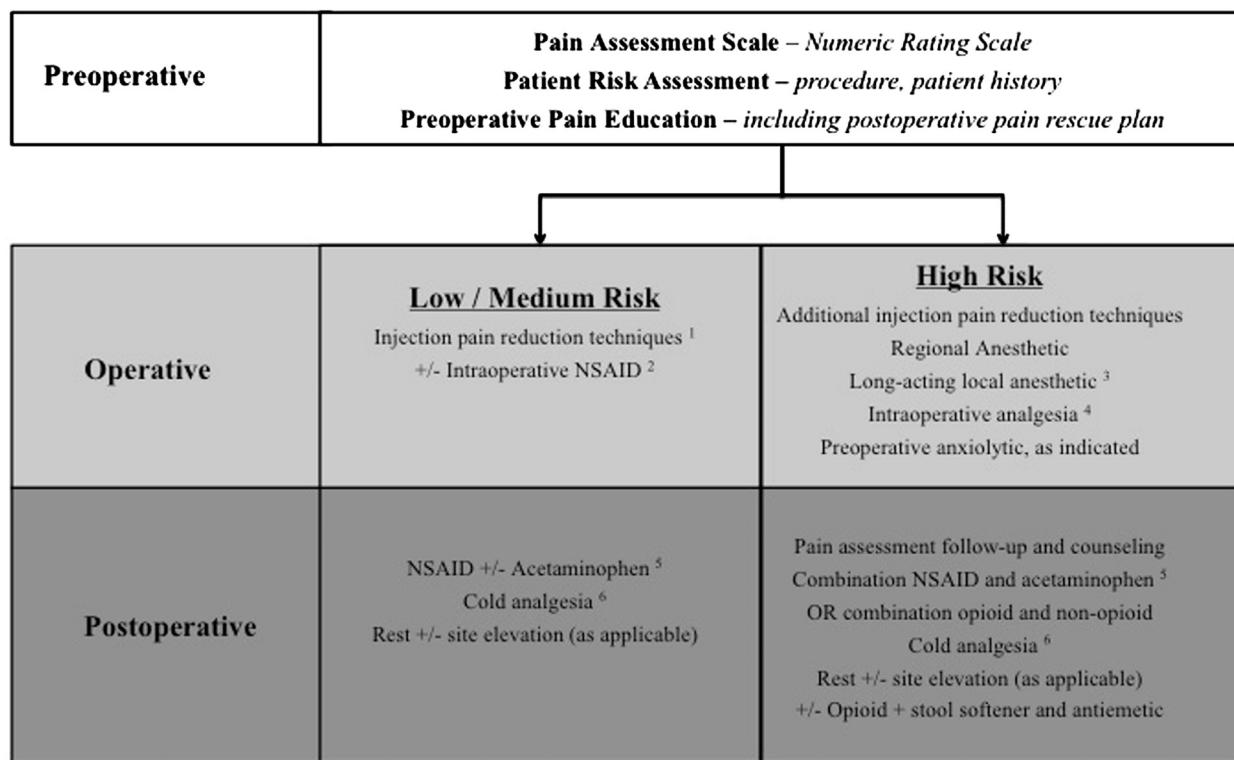
DISCUSSION

In conclusion, the use of local anesthesia techniques are now routine in office-based dermatology practice and have provided a strong foundation for safe perioperative pain management for minor procedures in an outpatient setting. The modern reality is that APSP is more than an inevitable unpleasant nuisance to “grin and bear” and not just a problem of other specialties. When a procedure, such as a laser therapy, an excision, or an advancement flap, is broken down to its constitutive components and when a patient is screened for risk factors, there are multiple opportunities and multiple treatments that can be used in concert to effectively attenuate a patient’s immediate and near term pain experience with no or minimal opioid use and reduction of postsurgical complications (Fig 3). Some procedures

that carry low APSP risk, such as obtaining a punch biopsy specimen, may only require limited intervention, such as buffering the lidocaine or vibration, to reduce the pain of the injection in a specifically at-risk patient. Other procedures with higher risks, such as an extensive rotation flap, may require more substantive interventions, such as multimodal and peri- and postoperative analgesia. A multimodal approach to patient-centered, APSP management is not new in medicine, but can be structured for dermatology patients. Acetaminophen and NSAIDs are effective backbones to this strategy. They can be used in combination with each other or with non-opioid or opioid adjuncts to improve patient outcomes, reduce unnecessary opioid use, and minimize the risks for hyperalgesia or other pain complications.

Given the number of procedures that dermatologists perform and, therefore, the increasing risk of APSP and its complications that dermatologists embrace, dermatologists should be at the forefront of acute pain research and pursue an integrated approach with other specialties. However, the vast majority of studies and discussions arise from other specialties, from dentistry to general surgery to, of course, anesthesiology.

Dermatologists can be at the forefront of furthering our understanding of cutaneous wound healing and understanding how new and traditional pharmacologic interventions, such as NSAIDs, affect collagen metabolism and bleeding in healing surgical sites. The other challenge for dermatology is to develop validated risk scales and clinical trials of specialty-based interventions that can be used for low-, medium-, and high-risk procedures and patients. In better delineating risk and refining pharmacologic and nonpharmacologic interventions, dermatologists can further decrease the risks associated with our treatments and improve patient outcomes and satisfaction both in the short term and in the long term.

¹ Buffered lidocaine, vibration, site cooling, or distraction.² Ibuprofen 400mg just after surgery³ Such as, bupivacaine or liposomal bupivacaine⁴ Celecoxib 200mg q12 h starting the night before or gabapentin 300-600mg 1-2h prior to surgery. Just after surgery, ibuprofen 400mg then q6h prn pain or acetaminophen 1000mg/ibuprofen 400mg then q6h prn pain⁵ Ibuprofen 400mg po 6h prn pain and/or Acetaminophen 1g po q6h prn pain OR Celecoxib 200mg po q12h prn pain⁶ Applied to the surgical site for 10-20 minutes every 1-4 waking hours as needed**Fig 3.** Acute postsurgical pain management algorithm.

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REFERENCES

- Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin.* 2014;30:149-160.
- Kurup V, Dabu-Bondoc S, Senior A, et al. Concern for pain in the pre-operative period- is the internet being used for information by patients? *Pain Pract* 2014;14:E69-E75.
- Parsons B, Schaefer C, Mann R, et al. Economic and humanistic burden of post-trauma and post-surgical neuropathic pain among adults in the United States. *J Pain Res.* 2013;6:459-469.
- Ledowski T, Stein J, Albus S, MacDonald B. The influence of age and sex on the relationship between heart rate variability, haemodynamic variables and subjective measures of acute post-operative pain. *Eur J Anaesthesiol.* 2011;28:433-437.
- Koo PJ. Addressing stakeholders' needs: economics and patient satisfaction. *Am J Health Syst Pharm.* 2007;64:S11-S15.
- Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg.* 2007;105:205-221.
- Ahn CS, Davis SA, Dabade TS, Williford PM, Feldman SR. Noncosmetic skin-related procedures performed in the United States: an analysis of national ambulatory medical care survey data from 1995 to 2010. *Dermatol Surg.* 2013;39:1912-1921.
- Limthongkul B, Samie F, Humphreys TR. Assessment of postoperative pain after Mohs micrographic surgery. *Dermatol Surg.* 2013;39:857-863.
- Firoz BF, Goldberg LH, Arnon O, Mamelak AJ. An analysis of pain and analgesia after Mohs micrographic surgery. *J Am Acad Dermatol.* 2010;63:79-86.
- Harris K, Curtis J, Larsen B, et al. Opioid pain medication use after dermatologic surgery: a prospective observational study of 212 dermatologic surgery patients. *JAMA Dermatol.* 2013;149:317-321.
- Bigliardi PL, Tobin DJ, Gaveriaux-Ruff C, Bigliardi-Qi M. Opioids and the skin—where do we stand? *Exp Dermatol* 2009;18:424-430.
- Vickers ER, Boocock H, Harris RD, et al. Analysis of the acute postoperative pain experience following oral surgery: identification of 'unaffected', 'disabled' and 'depressed, anxious and disabled' patient clusters. *Aust Dent J.* 2006;51:69-77.
- Nalamachu S. An overview of pain management: the clinical efficacy and value of treatment. *Am J Manag Care.* 2013;19: s261-s266.

Chronic pain management in dermatology

A guide to assessment and nonopioid pharmacotherapy

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Learning objectives

Describe important mechanisms/pathways and pathophysiology of pain states as they manifest in dermatologic conditions; assess patients' pain severity and discuss biopsychosocial factors that impact pain management (including treatment goals and selection of therapeutic agents); compare and contrast the expected efficacy and risk/benefit ratio of commonly prescribed non-opioid analgesics for individualized dermatologic therapy and pain management and develop individualized pain management strategies and set appropriate goals for patients' pain relief, functional improvement, and restoration of psychological health.

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Pain is a central component of illness and suffering, yet unfortunately it is frequently undertreated. In dermatology, many acute and chronic conditions are characterized by pain that may require therapeutic intervention in addition to medical treatment aimed at treating the primary disease. To date, however, there are limited recommendations or evidence in the published literature on pain and pain management strategies for patients with skin disease. In an effort to enable providers to more comprehensively and effectively treat chronic pain in the primary and multidisciplinary dermatologic context, these topics will be discussed in this 2-part continuing medical education article. Part I of this series will describe important mechanisms of pain and detail individualized chronic pain assessment and treatment strategies using nonopioid analgesia. (*J Am Acad Dermatol* 2015;73:563-73.)

Key words: hidradenitis suppurativa; nonsteroidal antiinflammatory drugs; opioid analgesia; pain management; postherpetic neuralgia.

Pain is one of the most common ailments that motivate patients to seek out medical care. It has been referred to as the "fifth vital sign," yet it is generally not documented quantitatively in routine medical care and unfortunately often remains undertreated. According to the Institute of Medicine's 2011 report "Relieving Pain in America," at least 100 million Americans are burdened with chronic pain. From an economic standpoint, pain impacts the

Abbreviations used:

COX:	cyclooxygenase
GI:	gastrointestinal
NSAIDs:	nonsteroidal antiinflammatory drugs
PHN:	postherpetic neuralgia
PPI:	protein-pump inhibitor
SNRIs:	serotonin norepinephrine reuptake inhibitors
TCAs:	tricyclic antidepressants

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entire health care system. It is associated with high utilization of health care, and its societal cost is compounded by the loss of productivity of affected individuals, estimated at \$61.2 billion annually based on a survey of 28,902 working adults conducted from August 2001 to July 2002.¹ Accordingly, a number of states have adopted continuing medical education requirements to facilitate knowledge regarding pain management for licensed physicians. Overall, pain represents a complicated and debilitating problem and continues to remain a significant public health concern.

Many dermatologic conditions are associated with pain. Pain management is often required for diseases of acute onset, including cellulitis and other skin infections, benign and malignant skin tumors, and acute burns and their chronic sequelae. Chronic conditions also may necessitate long-term adjunctive pain management in addition to treatment of the primary skin disease. For instance, reports have associated hidradenitis suppurativa, lichen planus, bullous dermatoses, venous insufficiency, lipodermatosclerosis, and lichen sclerosus et atrophicus with significant pain.²⁻⁶ Finally, systemic conditions treated by dermatologists, such as psoriasis, morphea, and systemic lupus erythematosus, can feature prominent, disabling pain either because of cutaneous symptoms or as a result of their multisystem involvement.⁷⁻¹⁰

To date, there is limited information regarding pain and pain management strategies for chronic dermatologic disorders. Dermatologists are often the principal providers guiding their patients' care both in a primary and multidisciplinary context. In an effort to enable providers to more comprehensively and effectively treat patients, we will discuss pain assessment and management in this continuing medical education article.

PAIN: ETIOLOGY AND PATHOPHYSIOLOGY

Key points

- **The manifestation and subjective experience of pain is variable but potentially debilitating, reflecting the interplay of several contributory factors**
- **Analgesia is a therapeutic mainstay that can provide patients with significant symptom relief**

Pain negatively affects all aspects of patients' lives, often giving rise to functional impairment, psychological distress, reduced productivity, and diminished quality of life. Ultimately, it functions potently as both a sensation and as an emotion.¹¹

Physiologically, the skin, muscle, tendons, and blood vessels are all innervated by somatosensory afferent neurons that are specialized to respond to noxious stimuli associated with potential tissue injury. "Nociception" refers to the sequence of electrochemical events that lead from the detection of tissue-damaging stimuli to the perception of pain. Pain is detected by 2 different types of peripheral nociceptive neurons. A-delta fibers are thinly myelinated and permit rapid conduction. C fibers are unmyelinated and conduct more slowly.¹² In normal tissues, nociceptors are silent in the absence of tissue injury. When the painful stimulus nears and exceeds the level where injury can occur, the rate of discharge of these neurons rises, reflecting the intensity of the noxious stimulus. Neuronal responses therefore not only signal the presence of pain but also encode its intensity.

Primary afferent pain fibers anatomically convey information about noxious stimuli via sensory ganglia to second-order neurons in the dorsal horn of the spinal cord. These then project upward to the contralateral ascending spinothalamic tract, which connects to thalamic neurons and ultimately the somatosensory cortex. Damage to these pathways results in a deficit of pain and temperature discrimination. It can also result in painful dysesthesias that characterize neuropathic pain. Descending pain-modulating circuits also play a major role on the perceived intensity of pain. These tracts, such as those via the midbrain periaqueductal gray, receive afferents from the frontal cortex and hypothalamus and project to rostroventral medullary neurons. These in turn project in the dorsolateral white matter of the spinal cord, terminating on dorsal horn neurons. Additional descending pathways arise from other brainstem nuclei, including the locus ceruleus and the dorsal raphe nucleus. Major neurotransmitters used by these circuits include endorphins, serotonin, and norepinephrine, underlying the rationale for treating pain with opioids and serotonin agonists, among other agents.¹³

Potentially debilitating pain is often caused by chronic tissue inflammation. When intense or prolonged stimuli are applied to damaged or inflamed tissues, the process of sensitization occurs. The threshold for activating primary afferent nociceptors is lowered, leading to an increased frequency of firing for all stimulus intensities.¹¹ Several factors, such as low pH and the presence of inflammatory mediators, such as leukotrienes, bradykinin, and some prostaglandins all play a significant role in sensitization. The result of this sensitization is the universally understood result of injury. The area that has been injured is immediately sensitized, such that

nonpainful stimuli (eg, light touch) now produce pain in the injured area, a phenomenon known as allodynia. When tissue heals normally, the allodynia resolves as the tissue heals; with repeated injury, the allodynia can be sustained even after the tissue has healed. The presence of persistent allodynia is one of the hallmarks of neuropathic pain. Moreover, the amplification of the response provoked by painful stimuli has been suggested as a causal factor in certain chronic pain conditions.¹⁴

Not uncommonly, patients report chronic pain in association with dermatologic conditions. It is imperative that clinicians perform a thorough assessment for pain in relevant contexts, as we will describe in the next section.

APPROACH TO PAIN ASSESSMENT

Key points

- **The manifestation and subjective experience of pain reflects the interplay of several contributory factors**
- **Analgesia is a therapeutic mainstay that can provide patients with significant symptom relief**

Many overlapping factors influence the perception of pain, from inflammation to psychosocial, neurobiologic, and genetic factors.^{11,12} During pain assessment, a thorough characterization of symptoms is recommended, taking into account the site, duration, temporal pattern, exacerbating and remitting factors, intensity, and type of pain. Additional factors contributing to suffering should also be considered, including concurrent medical conditions and psychosocial distress. Various validated assessment tools for regular self-reported assessment of pain exist. These can be useful adjuncts when formulating an effective individualized treatment plan.¹⁵ When determining whether pain is mild, moderate, or severe, the Brief Pain Inventory is a validated, widely used, and simple self-administered questionnaire that can offer insight into pain severity and impact on daily function.^{16,17} This tool uses simple numeric rating scales ranging from 0 to 10. It was developed by the Pain Research Group of the World Health Organization Collaborating Centre, and has demonstrated validity and reliability across cultures and languages.¹⁷ Clinicians can use the Brief Pain Inventory to determine overall pain severity. This is defined by the “worst pain score,” calculated as the arithmetic mean of the 4 severity items on the questionnaire. Mild pain is defined by a score of 1 to 4, moderate pain by a score of 5 to 6, and severe pain by a score of 7 to 10.¹⁶⁻¹⁸

Pain assessment can broadly be subdivided into 2 approaches for acute treatment and chronic pain management. In this article, we discuss the management of chronic pain. This requires multidisciplinary approaches, including interventional procedures, physical rehabilitation, and cognitive behavioral therapy. Nonetheless, drug therapy often plays an important role in this clinical setting. Common agents will most often produce relief, but—depending on the nuances of each clinical scenario—a multidisciplinary approach to analgesic selection may be necessary for effective pain management.

When choosing medications, both safety and clinical efficacy must be considered. The World Health Organization recommends that clinicians conservatively approach analgesia by using non-opioid agents before a trial of opioid therapy unless the pain is severe.¹⁹ Some patients will require long-term and/or high-dose analgesic therapy, which complicates pain management.²⁰ In such cases, referral to a specialist with expertise to guide pain management is advised. As we will discuss, when choosing which analgesic modalities will be most effective for chronic pain, clinicians must carefully balance the goal of effective pain relief with each agent's risks for potential complications.

NONOPIOID ANALGESICS: NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND ACETAMINOPHEN

Key points

- **Given the relatively favorable tolerability, efficacy, and adverse effect profile of nonsteroidal antiinflammatory drugs and acetaminophen, these agents are attractive initial options to treat pain**
- **Unless contraindicated, management of all levels of pain (from mild to severe) includes a drug from this category**
- **When prescribing these agents, clinicians should carefully assess potential risk factors for toxicity and consider that certain patients may have difficulty tolerating them for longer-term analgesia**

Nonsteroidal antiinflammatory drugs (NSAIDs) encompass a diverse group of medications with the capacity to suppress signs and symptoms of inflammation. They are available over the counter and by prescription in the United States. By inhibiting cyclooxygenase (COX) enzymes, NSAIDs block prostaglandin biosynthesis to varying degrees.^{20,21} NSAIDs are principally used for pain of low to moderate intensity, such as sunburn and palmar psoriasis. There are many NSAIDs from which to choose

Table I. Nonopioid analgesics and typical doses for pain relief¹¹

Generic name	Dosing guideline	Comments
Aspirin	650 mg PO q4h	Enteric-coated preparations available
Acetaminophen	650 mg PO q4-6h	Avoid doses >3000 mg/day given risk of hepatotoxicity
Ibuprofen	400 mg PO q4-6h	Available without a prescription
Naproxen	250-500 mg PO q12h	
Fenoprofen	200 mg q4-6h	Contraindicated in renal disease
Ketorolac	15-60 mg IM/IV q4-6h	Available for parenteral use
Celecoxib	100-200 mg PO q12-24h	COX-2 selective inhibitor

All nonsteroidal antiinflammatory drugs can potentially cause renal failure or contribute to the worsening of preexisting renal disease. These agents should be used with caution in patients with renal, hepatic, or cardiovascular disease or risk. COX, Cyclooxygenase; IM, intramuscular; IV, intravenous; PO, per os; q4h, every 4 hours; q6h, every 6 hours; q12h, every 12 hours; q24h, once daily.

(Table I), but there is little literature to substantiate the efficacy of one agent over another.²² Differences in response to various agents have been noted. These have been observed among individuals treated with the same NSAID and within individuals treated with different NSAIDs—even when the drugs are structurally related. A therapeutic trial of 1 to 2 weeks is therefore recommended, which may be continued if patients achieve a satisfactory response; combination therapy with >1 NSAID, however, should be avoided.²¹

NSAIDs as a class are considered relatively safe drugs that share therapeutic characteristics and adverse effects—the latter of which are thought to be dose-dependent and related to COX enzyme inhibition. Burmester et al²³ published a systematic analysis on the opinions of a multidisciplinary panel of 18 experts from 10 European nations on the appropriateness of using 5 NSAIDs with or without a proton pump inhibitor (PPI) for the treatment of rheumatic disease. The agents studied included selective and nonselective NSAIDs: ibuprofen, diclofenac, naproxen, celecoxib, and etoricoxib. The conclusions drawn by their analysis were consistent with previous consensus statements and recommended individualized treatment based on the degree of gastrointestinal (GI) and cardiovascular risk. One hundred forty-four clinical scenarios were assessed using an electronic rating program to provide a consensus on the appropriateness of selected analgesic options. Patient risk factors included age, cardiovascular risk, aspirin use, GI risk, and the use of anticoagulants or corticosteroids. Naproxen was favored in the presence of cardiovascular risk factors, whereas COX2 inhibitors (sometimes with a PPI) or nonselective NSAIDs in addition to a PPI were recommended for those with GI risk factors. For patients with elevated GI and cardiovascular risk, the use of any NSAID was discouraged.^{23,24} These findings are summarized in Table II. The interactive

electronic tool is accessible to aid in decision-making, so that individual providers may assess a relevant clinical scenario and compare their conclusions with the consensus opinion of the panel.²⁵

For chronic or continuous dosing of NSAIDs, laboratory monitoring is recommended, consisting of a complete blood cell count and measurements of blood urea nitrogen, creatinine, and aspartate aminotransferase at least once yearly. In patients with increased risk for adverse effects, including patients with conditions such as anemia, renal compromise, and drug-related hepatotoxicity, monitoring may be performed more frequently. The duration of NSAID therapy and concomitant medications, such as the use of diuretics and angiotensin-converting enzyme inhibitors, may also necessitate closer safety monitoring, including increased visit frequency and laboratory testing.^{26,27} Methotrexate for example, is often coadministered with NSAIDs despite concern surrounding its overlapping adverse effect profile and potential accumulation of methotrexate in the setting of NSAID use. A systematic review of the available literature on rheumatoid arthritis found that concurrent NSAID use is safe provided that appropriate laboratory monitoring is in place. Antiinflammatory dosing of concomitant aspirin, however, was not recommended because of the potential adverse effects on liver and renal function.²⁸ Recommendations regarding cyclosporine are similar to those for methotrexate coadministration with NSAIDs. Other medications, however—including warfarin, phenytoin, and lithium—may pose relative contraindications to NSAID use and warrant referral to an appropriate specialist.²⁹

With chronic NSAID use, GI adverse effects ranging from dyspepsia to peptic ulcer disease are most commonly reported and are estimated to affect 15% to 30% of regular users.²¹ For patients at high risk, a prophylactic gastroprotective agent is

Table II. Guidelines for selection of nonsteroidal antiinflammatory drug therapy in patients with cardiovascular and gastrointestinal risk factors²⁵

Cardiovascular risk*	No or low gastrointestinal risk	Increased gastrointestinal risk†
No cardiovascular risk, no aspirin use	Nonselective NSAIDs (eg, ibuprofen, diclofenac, and naproxen)	COX-2 selective inhibitor (eg, celecoxib or etoricoxib) or nonselective NSAID and PPI <ul style="list-style-type: none"> • Use COX-2 selective inhibitor and PPI in those with previous GI bleeding
Cardiovascular risk, with or without aspirin use	Naproxen plus PPI	Avoid any NSAID if possible If needed: <ul style="list-style-type: none"> • Diclofenac/naproxen plus PPI • COX-2 selective inhibitor plus PPI

COX, Cyclooxygenase; GI, gastrointestinal; PPI, proton pump inhibitor; NSAID, nonsteroidal antiinflammatory drug.

*Ten-year risk of fatal cardiovascular event (low, <10% risk; high, ≥10% risk).

†Increased GI risk is related to the number of risk factors present: previous GI event, ≥65 years of age, continuous NSAID use, and concomitant use of aspirin/anticoagulants/corticosteroids.

recommended when beginning NSAID therapy. Although few comparative studies exist, the current evidence suggests that PPIs and misoprostol are superior to ranitidine for the prevention of duodenal ulcers (relative risk, 0.29 [95% confidence interval, 0.15-0.56]) but not gastric ulcers.^{30,31} Potentially significant renal side effects, hypersensitivity reactions, and an increased risk of cardiovascular events are also associated with NSAID use. These potential complications necessitate close monitoring or avoidance of NSAIDs in patients with relevant history and/or risk factors.^{20,32,33}

Acetaminophen is another widely used pain relief agent; it is thought to potentially inhibit prostaglandin production in the central nervous system.²¹ It is not a suitable substitute for NSAIDs in chronic inflammatory conditions, but acetaminophen is well tolerated with a low incidence of GI-related side effects. Acute overdoses can produce severe hepatic damage. In otherwise healthy adults, the maximum recommended daily dose (using 500 mg tablets) has recently been lowered by some manufacturers to 3000 mg. Concomitant liver disease and alcohol abuse are both considered relative contraindications to the use of acetaminophen. Since acetaminophen can be found in many products, care must be taken to avoid inadvertent overdose.

In general, NSAIDs are safe in low-risk patients and are attractive options for the initial management of mild to moderate pain because they are well tolerated and effective. Acetaminophen is also a useful adjunct in those patients without risks for hepatotoxicity. Increasing the dose of any agent is nevertheless associated with increased risk of toxicity. If these agents prove ineffective, modification of the analgesic regimen may be required for satisfactory pain relief.

USE OF ANTIDEPRESSANTS AND ANTICONVULSANTS AS ANALGESICS

Key points

- Tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors provide pain relief distinct from their antidepressant effects
- Antiepileptic agents may be a useful adjunct for neuropathic pain, however in the absence of such symptoms their role is less clear

A number of antidepressants possess analgesic properties that are distinct from their psychotropic effects (Table III).³⁴ When used for chronic pain, tricyclic antidepressants (TCAs) are often prescribed at lower doses than those used to treat depression (25-100 mg nortriptyline or equivalent).^{34,35} In general, TCAs should be started at the lowest effective dose and carefully titrated upward. The decision to initiate TCAs should take into account risk factors for cardiotoxicity and other class-specific side effects (eg, anticholinergic symptoms, including confusion, urinary retention, postural hypotension, and dry mouth), particularly in elderly patients.³⁶ In the literature, a screening electrocardiogram (ECG) is recommended for patients who are beginning to take TCAs and who are ≥40 years of age. Younger patients may be screened by history for cardiac disease and do not require an ECG if the history is negative. Pertinent questions about known heart disease, syncope, chest pain, palpitations, shortness of breath, and dyspnea on exertion are relevant. In addition, family history of heart disease (including sudden death, cardiac dysrhythmias, and/or conduction disturbances) should be obtained. The most common electrocardiographic changes caused by TCAs include nonspecific ST-T changes and

Table III. Antidepressants, anticonvulsants, and typical doses for analgesia³⁶

Medication class	Starting dose	Titration	Maximum dosage	Duration of adequate trial
Secondary amine TCAs (preferred, use tertiary amine TCA only if secondary not available)				
Nortriptyline and desipramine	25 mg at bedtime	Increase by 25 mg/day every 3-7 days as tolerated	150 mg/day; if blood level of active medication and its metabolite is <100 ng/mL (mg/mL), continue titration with caution	6-8 wks with at least 2 wks at maximum tolerated dosage
SNRIs				
Duloxetine	30 mg/day	Increase to 60 mg once daily after 1 wk	60 mg twice daily	4 wks
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each wk	225 mg daily	4-6 wks
Calcium channel α 2- δ ligands				
Gabapentin	100-300 mg total daily, dosed at bedtime or divided 3 times/day	Increase total dose by 100-300 mg every 1-3 days as tolerated, divided for BID or TID dosing (proceed slowly in elderly)	Usual effective total dose 900-3600 mg daily; recommended dosing is 300-1200 mg TID. Reduce if impaired renal function	3-8 wks for titration plus 2 wks at maximum dosage
Pregabalin	50 mg tid or 75 mg bid	Increase to 300 mg daily after 3-7 days, then by 150 mg/d every 3-7 days as tolerated	600 mg daily (200 mg three times or 300 mg twice daily); reduce if impaired renal function	4 wks

BID, Two times daily; TID, three times daily; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

prolongation of the QT interval, PR interval, and QRS duration. In the setting of preexisting conduction abnormalities (particularly bundle branch block) and structural heart disease, a screening ECG can identify patients who are at increased risk for toxicity.^{37,38}

Caution should be exercised when prescribing TCAs to patients who take certain medications, including selective serotonin reuptake inhibitors and medications that inhibit cytochrome P450, or to patients who are at risk for overdose, because supratherapeutic plasma levels are potentially lethal. Similarly, other populations that are at higher risk for TCA-related adverse effects include patients with ischemic cardiovascular disease, ventricular conduction abnormalities, glaucoma, underlying urinary retention, and autonomic neuropathy. In these select populations, dosages should be limited to <100 mg per day when possible, with close therapeutic monitoring.^{34,36,37} For safety monitoring, serum levels of TCAs are useful. These markers are used to establish the proper dose in depression but can also assist in reducing toxicity and assessing adherence in pain management—levels should be drawn once the drug is in steady state (≥ 5 days after a dose change, or longer in

elderly patients) and at trough (immediately before the next dose).³⁹⁻⁴¹ A complete review of systems, including questions about mood changes, suicidal ideation, and behavioral changes is pertinent to conduct while monitoring patients who are taking TCAs. Rarely, TCAs have been associated with bone marrow and liver toxicity; however, additional baseline or routine monitoring, such as repeat ECG measurements, blood cell counts, and liver function tests is not recommended in the absence of specific clinician concerns. In general, 6 to 8 weeks of therapy may be required for an adequate analgesic trial of TCAs, including 2 weeks at the highest dose tolerated.³⁶

SNRIs, particularly duloxetine and venlafaxine, have also shown benefit in the treatment of neuropathic pain. These agents have a relatively favorable side effect profile compared to TCAs. In addition, certain antiepileptic drugs, including gabapentin, pregabalin, and carbamazepine, are thought to reduce the central nervous system hyperresponsiveness underlying chronic pain, and are now approved by the US Food and Drug Administration for the treatment of neuropathic pain.⁴²⁻⁴⁴ Gabapentin and pregabalin bind to the alfa2-delta subunit of voltage-gated calcium

channels, decreasing the release of glutamate, norepinephrine, and substance P.³⁶ In select cases, such as patients with trigeminal neuralgia and postherpetic neuralgia (PHN), antidepressants and anticonvulsants have demonstrated benefit when pain is primarily neuropathic. In the absence of neuropathic symptoms, there is little research clarifying the role of these agents in pain management for dermatologic disease.

PHN is a hallmark condition treated by dermatologists for which the analgesic mainstays are antidepressant and anticonvulsant agents. This debilitating, chronic presentation of neuropathic pain affects 10% to 15% of patients who have herpes zoster. PHN can persist long beyond the resolution of cutaneous symptoms.^{45,46} It can be challenging to manage, and milder analgesics, including aspirin and other NSAIDs, are thought to be of limited therapeutic value for analgesia in both acute and chronic settings.⁴⁷ Randomized trials have suggested that medications—including TCAs, anticonvulsant agents (both gabapentin and pregabalin), opioids, the lidocaine 5% patch, and topical capsaicin—can effectively reduce pain in monotherapy or in combination.⁴⁷ TCAs had been considered first-line therapy, but since becoming approved for this indication, gabapentin and the lidocaine patch are also currently recommended, offering superior tolerability profiles over TCAs. Factors to guide the selection of medication include additional patient comorbidities, the potential for adverse effects, and physician and patient preference.³⁶

In clinical trials, 47% to 67% of patients treated with TCAs for PHN report moderate to excellent pain relief.⁴⁸ Nortriptyline is the preferred agent over amitriptyline because of fewer side effects based on the results of a randomized, double-blind crossover trial.^{48,49} Desipramine also may be used, and has the fewest side effects of the first-generation TCAs. It demonstrated efficacy in 1 small study of 26 patients at a mean dose of 167 mg per day.⁵⁰

Randomized controlled trials have also demonstrated the efficacy and safety of gabapentin and pregabalin for PHN.^{51,52} Gabapentin is generally safe, without clinically important drug interactions. Its availability in generic formulation makes it a commonly chosen agent in the treatment of PHN. Pregabalin requires dose reduction in patients with renal impairment, and because it is a newer drug, its long-term safety is not as established as that of gabapentin. Pregabalin, however, has shown anxiolytic effects, which may complementarily benefit patients with chronic pain.^{36,52} Both gabapentin

and pregabalin are associated with dose-dependent side effects, including somnolence, dizziness, and peripheral edema, which can be reduced by gradual dose titration.

Topical agents, including lidocaine 5% patch, also offer a beneficial therapeutic strategy for patients with localized peripheral neuropathic symptoms. Mild skin reactions are the only reported adverse effects, as later in this article.³⁶ Other potential treatments for PHN include opioids as monotherapy or in combination and capsaicin cream. Combination therapy, such as gabapentin and nortriptyline, is standard in clinical practice and possibly more effective than single-agent therapy for PHN. It does, however, confer a greater risk of side effects.^{47,48} Initial dosing regimens and guidelines for analgesia with antidepressants and anticonvulsants are presented in Table III.

Unfortunately, PHN and other neuropathic pain syndromes are challenging to treat, and most therapies commonly produce significant side effects with unknown long-term benefits. Despite adequate trials of first- and second-line therapies, patients may continue to suffer refractory, ongoing pain. Referral to a pain specialist is recommended in such cases.

TOPICAL AGENTS AND ALTERNATIVE METHODS OF PAIN RELIEF

Key point

- Commonly used topical agents for the treatment of nociceptive pain include nonsteroidal antiinflammatory drugs, capsaicin, or local anesthetics, which confer the advantage of avoiding the systemic side effects associated with oral analgesics

Topical administration of anesthetics and analgesics can provide efficient and painless delivery of medications with reduced potential for systemic side effects. Moreover, topical anesthetic agents can be invaluable to increase patient comfort in a convenient and targeted fashion for acute pain settings. The benefits of topical drug delivery include the potential for localized therapeutic drug levels, ease of dose titration and termination, improved patient adherence, and direct access to the target site.

For localized and relatively mild pain, a topical agent may be a reasonable analgesic choice, especially in patients who cannot tolerate oral therapy. A summary of common available agents, with their features and dosing, is available in Table IV.

The lidocaine 5% patch has been used with efficacy in a variety of neuropathic pain conditions,

Table IV. Common topical analgesics and anesthetics for treatment of chronic pain⁵⁴⁻⁶⁶

Drug	Features	Use	Adult dosing
Capsaicin	Patch, gel, or cream; attenuates pain via counterirritant mechanism; skin irritation is common and may diminish after 1-2 wks	Neuropathic and MSK pain	Available in low concentrations (0.025-0.075%) and 8% formulation; apply to affected area several times daily as tolerated; 8% patch (PHN and HIV neuropathic pain) intended for 1-time use
Lidocaine 5%	10-14 cm patch; slow-release analgesia; reduces sensation; ineffective for procedural pain	Neuropathic pain (including PHN) and MSK pain	Apply up to 3 patches for up to 12 hrs within a 24-hr period, only to intact skin; cover most painful areas
Menthol and menthol salicylates	Gel, cream, and ointment; functions as a counterirritant and has vasodilatory effects	MSK pain	Apply cream/gel liberally to affected area and massage; apply patch every 12 hrs
Topical NSAIDs (eg, diclofenac, ketoprofen, and ibuprofen)	Patch, gel, cream, and plaster; proposed to have similar efficacy to oral formulations with a more favorable safety profile	MSK pain	Note that individual labels vary: for example, diclofenac 0.1% gel should be measured (2-4 g) and massaged into the affected area, applying ≤4 times/day

4% Lidocaine is available in a cream formulation. It is not covered in this table because its use is limited to the management of acute pain. MSK, Musculoskeletal; NSAID, nonsteroidal antiinflammatory drug; PHN, postherpetic neuralgia.

including PHN, diabetic polyneuropathy, and post-amputation pain.^{36,53} Often 7 to 10 days of treatment are required before efficacy is noted. Lidocaine is also available in a 4% cream formulation, however evidence supporting its use is limited to settings of acute pain management. Systemic toxicity is not considered a significant risk in adults. Side effects are usually limited to skin irritation, which may necessitate the discontinuation of treatment.⁵⁴

Topical NSAIDs have been studied primarily in the setting of musculoskeletal disease. When administered topically, these agents have been shown to accumulate in high concentrations in the dermis, and also achieve levels in muscle that are at least equivalent to those achieved with systemic NSAID administration. Adverse drug reactions affect up to 15% of patients. Although cutaneous reactions account for the majority of such reactions, GI effects have been rarely noted.⁵⁵⁻⁵⁷ Based on a large metaanalysis, ketoprofen may be the most effective topical NSAID for acute pain, but diclofenac (in topical solution and gel) has been shown to be superior to placebo in trials of osteoarthritis.⁵⁸⁻⁶⁰

Topical capsaicin preparations are derived from chili peppers and have demonstrated analgesia via a counter-irritant mechanism, whereby the irritation of a painful zone attenuates the sensation of pain. Topical capsaicin showed superiority to placebo in both musculoskeletal and neuropathic pain conditions.^{61,62} Capsaicin is a transient receptor potential

cation channel, subfamily V, member 1 agonist that first activates cutaneous nociceptive nerve fibers. This activation provokes the release of substance P, stimulating neurogenic inflammation. These events are followed by reversible defunctionalization of nerve ends and the inhibition of pain transmission.^{63,64} Low concentration (0.025% and 0.075%) cream formulations have shown mild efficacy in neuropathic pain; these agents may require several weeks of application for a noticeable effect. An 8% capsaicin patch is also available for use in patients with PHN and HIV neuropathic pain.^{56,65} The most often encountered adverse effect is burning pain at the site of application, which may mitigate after 1 to 2 weeks of continued use. Although topical capsaicin is generally not considered a satisfactory monotherapy for chronically painful conditions, it can be a helpful adjuvant agent—particularly when pain is primarily neuropathic.⁵⁶

Topical NSAIDs, lidocaine, and capsaicin have been shown to effectively reduce pain in certain settings.^{42,66-69} There is evidence to support the use of these and other anesthetic agents, particularly in the treatment of acute or postprocedural pain. Unfortunately, these analgesics may be difficult to incorporate in the chronic dermatologic setting if patients are already using topical medication(s) to treat their primary disease. Nonetheless, topical agents may beneficially supplement patients' existing analgesic regimen. Finally, alternate

modalities—including acupuncture, biofeedback, hypnosis, and cognitive behavioral therapy—have been used with success in select patients, both as alternative or complementary therapy.⁷⁰⁻⁷²

In conclusion, pain is a significant issue for many dermatology patients, which may represent the effects of primary skin disease and/or the systemic sequelae underlying the cutaneous manifestation. Chronic pain can be a particular challenge to adequately treat, consisting of nociceptive and/or neuropathic symptoms. For patients with mild to moderate chronic nociceptive pain, appropriate initial management may consist of NSAIDs and acetaminophen. Topical agents may also be beneficial as supplemental modalities or alone, with the advantage of avoiding the systemic side effects associated with oral analgesics. For neuropathic pain symptoms, certain psychotropic agents alone or as adjuncts can be beneficial. In select situations, when the severity of pain exceeds the analgesic capacity of a chosen regimen, escalation of therapy to include opioid agents may be warranted. Part II of this 2-part continuing medical education article details guidelines for initiating and comprehensively monitoring opioid therapy for chronic pain.

REFERENCES

1. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290:2443-2454.
2. Dufour DN, Emtestam L, Jemec GB. Hidradenitis suppurativa: a common and burdensome, yet under-recognised, inflammatory skin disease. *Postgrad Med J*. 2014;90:216-221. quiz 20.
3. Cheng S, Kirtschig G, Cooper S, Thornhill M, Leonardi-Bee J, Murphy R. Interventions for erosive lichen planus affecting mucosal sites. *Cochrane Database Syst Rev*. 2012;2:CD008092.
4. Bickle K, Roark TR, Hsu S. Autoimmune bullous dermatoses: a review. *Am Fam Physician*. 2002;65:1861-1870.
5. Nicholls SC. Sequelae of untreated venous insufficiency. *Semin Intervent Radiol*. 2005;22:162-168.
6. Simpson RC, Thomas KS, Murphy R. Outcome measures for vulval skin conditions: a systematic review of randomized controlled trials. *Br J Dermatol*. 2013;169:494-501.
7. Naversen DN, Trask DM, Watson FH, Burkett JM. Painful tumors of the skin: "LEND AN EGG". *J Am Acad Dermatol*. 1993;28:298-300.
8. Das S, Bernstein I, Jacob H. Correlates of self-reported quality of life in adults and children with morphea. *J Am Acad Dermatol*. 2014;70:904-910.
9. Guenther LC. Alefacept is safe and efficacious in the treatment of palmar plantar pustulosis. *J Cutan Med Surg*. 2007;11:202-205.
10. Iannuccelli C, Spinelli FR, Guzzo MP, et al. Fatigue and widespread pain in systemic lupus erythematosus and Sjögren's syndrome: symptoms of the inflammatory disease or associated fibromyalgia? *Clin Exp Rheumatol*. 2012;30:117-121.
11. Rathmell JP, Fields HL. Pain: Pathophysiology and Management. In: Fauci A, Longo DL, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 2012.
12. Bennett GJ. Update on the neurophysiology of pain transmission and modulation: focus on the NMDA-receptor. *J Pain Symptom Manage*. 2000;19:S2-S6.
13. Lomen-Hoerth C, Messing R. Chapter 7: Nervous System Disorders. In: McPhee S, Hammer G, eds. *Pathophysiology of Disease*. New York, NY: McGraw-Hill; 2010.
14. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci*. 2003;26:696-705.
15. Ripamonti CI. Pain management. *Ann Oncol*. 2012;23(Suppl 10):x294-x301.
16. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain*. 2004;20:309-318.
17. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23: 129-138.
18. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain*. 1995;61:277-284.
19. Yaksh TL, Wallace MS. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollman BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw-Hill; 2011.
20. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115:1634-1642.
21. Grosser T, Smyth E, Fitzgerald GA. Anti-inflammatory, antipyretic, and analgesic agents; pharmacotherapy of gout. In: Brunton LL, Chabner BA, Knollman BC, eds. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*. New York: McGraw-Hill; 2011.
22. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Nonsteroidal anti-inflammatory drugs for low back pain: an updated Cochrane review. *Spine (Phila Pa 1976)*. 2008;33: 1766-1774.
23. Burmester G, Lanas A, Biasucci L, et al. The appropriate use of non-steroidal anti-inflammatory drugs in rheumatic disease: opinions of a multidisciplinary European expert panel. *Ann Rheum Dis*. 2011;70:818-822.
24. Abramson SB. Clinical guidelines: Expert recommendations for NSAID use: a user-friendly model? *Nat Rev Rheumatol*. 2011;7:133-134.
25. Ismar Healthcare. Appropriate use of (non-)selective NSAIDs in chronic rheumatic disease. 2010. Available from: URL: <http://www.e-hims.com/Sensar/>. Accessed May 1, 2014.
26. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum*. 2000;43:1905-1915.
27. Patino FG, Olivieri J, Allison JJ, et al. Nonsteroidal antiinflammatory drug toxicity monitoring and safety practices. *J Rheumatol*. 2003;30:2680-2688.
28. Colebatch AN, Marks JL, van der Heijde DM, Edwards CJ. Safety of nonsteroidal antiinflammatory drugs and/or paracetamol in people receiving methotrexate for inflammatory arthritis: a Cochrane systematic review. *J Rheumatol Suppl*. 2012;90:62-73.

29. Kovarik JM, Mueller EA, Gerbeau C, Tarral A, Francheteau P, Guerret M. Cyclosporine and nonsteroidal antiinflammatory drugs: exploring potential drug interactions and their implications for the treatment of rheumatoid arthritis. *J Clin Pharmacol.* 1997;37:336-343.
30. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev.* 2002;(4):CD002296.
31. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther.* 2013;15(Suppl 3):S5.
32. Schlondorff D. Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int.* 1993;44:643-653.
33. Furst DE, Anderson W. Differential effects of diclofenac and aspirin on serum glutamic oxaloacetic transaminase elevations in patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum.* 1993;36:804-810.
34. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *Gen Hosp Psychiatry.* 2009;31:206-219.
35. Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. *Spine (Phila Pa 1976).* 2003;28:2540-2545.
36. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132:237-251.
37. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc.* 2010;85:S3-S14.
38. Smith A, Book W. Chapter 94. Effect of noncardiac drugs, electricity, poisons, and radiation on the heart. In: Fuster V, Walsh R, Harrington R, eds. *Hurst's The Heart.* New York, NY: McGraw-Hill; 2011.
39. Linder MW, Keck PE. Standards of laboratory practice: anti-depressant drug monitoring. National Academy of Clinical Biochemistry. *Clin Chem.* 1998;44:1073-1084.
40. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol.* 2001;52(Suppl 1):455-54S.
41. Baumann P, Hiemke C, Ulrich S, et al. The AGNP-TDM expert group consensus guidelines: therapeutic drug monitoring in psychiatry. *Pharmacopsychiatry.* 2004;37:243-265.
42. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet.* 2011;377:2226-2235.
43. Wallace MS. Pharmacologic treatment of neuropathic pain. *Curr Pain Headache Rep.* 2001;5:138-150.
44. Sullivan MD, Robinson JP. Antidepressant and anticonvulsant medication for chronic pain. *Phys Med Rehabil Clin N Am.* 2006;17:381-400. vi-vii.
45. Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. *Am J Clin Dermatol.* 2013;14:77-85.
46. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Neurology QSSotAAo. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2004;63:959-965.
47. Cohen JI. Clinical practice: Herpes zoster. *N Engl J Med.* 2013;369:255-263.
48. Tyring SK. Management of herpes zoster and postherpetic neuralgia. *J Am Acad Dermatol.* 2007;57:S136-S142.
49. Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology.* 1998;51:1166-1171.
50. Kishore-Kumar R, Max MB, Schafer SC, et al. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther.* 1990;47:305-312.
51. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA.* 1998;280:1837-1842.
52. Dworkin RH, Corbin AE, Young JP, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60:1274-1283.
53. Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. *Clin J Pain.* 2000;16:205-208.
54. Campbell BJ, Rowbotham M, Davies PS, Jacob P, Benowitz NL. Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster. *J Pharm Sci.* 2002;91:1343-1350.
55. Heyneman CA, Lawless-Liday C, Wall GC. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs.* 2000;60:555-574.
56. Sawynok J. Topical and peripherally acting analgesics. *Pharmacol Rev.* 2003;55:1-20.
57. McPherson ML, Cimino NM. Topical NSAID formulations. *Pain Med.* 2013;14(Suppl 1):S35-S39.
58. Haroutunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. *Pain Med.* 2010;11:535-549.
59. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2004;5:28.
60. Banning M. Topical diclofenac: clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. *Expert Opin Pharmacother.* 2008;9:2921-2929.
61. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ.* 2004;328:991.
62. Casanueva B, Rodero B, Quintial C, Llorca J, González-Gay MA. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatol Int.* 2013;33:2665-2670.
63. Irving GA, Backonja MM, Dunteman E, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med.* 2011;12:99-109.
64. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2013;2:CD007393.
65. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. *Eur J Clin Pharmacol.* 1994;46:517-522.
66. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev.* 2012;9:CD007400.
67. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clin Proc.* 2009;84:274-280.
68. Higashi Y, Kiuchi T, Furuta K. Efficacy and safety profile of a topical methyl salicylate and menthol patch in adult patients with mild to moderate muscle strain: a randomized,

- double-blind, parallel-group, placebo-controlled, multicenter study. *Clin Ther.* 2010;32:34-43.
69. Mina R, Melson P, Powell S, et al. Effectiveness of dexamethasone iontophoresis for temporomandibular joint involvement in juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2011;63:1511-1516.
70. Palermo TM, Eccleston C, Lewandowski AS, Williams AC, Morley S. Randomized controlled trials of psychological therapies for management of chronic pain in children and adolescents: an updated meta-analytic review. *Pain*. 2010;148:387-397.
71. Windmill J, Fisher E, Eccleston C, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database Syst Rev*. 2013;9:CD010323.
72. Wang C, de Pablo P, Chen X, Schmid C, McAlindon T. Acupuncture for pain relief in patients with rheumatoid arthritis: a systematic review. *Arthritis Rheum*. 2008;59:1249-1256.

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Chronic pain management in dermatology

Pharmacotherapy and therapeutic monitoring with opioid analgesia

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Learning objectives

Describe the clinical settings in which it may be appropriate to initiate opioid therapy for the management of chronic pain, in particular for pain states that manifest in dermatologic conditions, and discuss appropriate therapeutic goals; assess patients' pain to select an appropriate opioid agent and dosing regimen, with close attention to minimizing treatment-related side effects; discuss the safe and effective titration of analgesic dosing after initiating opioid therapy, including the consideration of opioid rotation, referral to a specialist in pain management, and/or discontinuation of therapy as indicated and describe components of routine therapeutic monitoring and discuss the signs of aberrant drug-related behavior.

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A number of chronic dermatologic conditions may necessitate long-term adjunctive pain management in addition to treatment of the primary skin disease, such as hidradenitis suppurativa, lichen planus, and other systemic diseases associated with significant pain. Adequate management of chronic pain can represent a unique challenge, but remains an integral component of clinical treatment in relevant contexts. For nociceptive pain of moderate to severe intensity, opioid analgesics can be beneficial when other pain management strategies have failed to produce adequate relief. The decision to initiate long-term opioid therapy must be carefully weighed, and individualized treatment plans are often necessary to effectively treat pain while minimizing adverse effects. Part II of this 2-part continuing medical education article will describe the appropriate settings for initiation of opioid analgesia for dermatology patients and detail therapeutic strategies and patient monitoring guidelines. (J Am Acad Dermatol 2015;73:575-82.)

Key words: nonsteroidal antiinflammatory drugs; opioid analgesia; pain; postherpetic neuralgia.

Chronic pain is extremely common, and by definition is persistent and often difficult to treat. In the dermatologic context, pain in addition to primary disease burden can confer

Abbreviations used:

FDA: US Food and Drug Administration
NSAID: nonsteroidal antiinflammatory drug

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significant quality of life impairment and morbidity for affected patients. For centuries, opioid analgesia has remained a mainstay of pain management, and its efficacy is well-established. For nociceptive pain of moderate to severe intensity, opioids can be useful when other analgesics fail to produce adequate relief. In the appropriate clinical context, with reasonable precautions and monitoring in place, opioid analgesia can be an effective and safe tool to treat refractory pain.

The use of opioid therapy has increased substantially in recent decades, particularly in the treatment of noncancer-related chronic pain. Global data reveal that the average opioid (morphine equivalent) consumption increased from 1.82 mg per person in 1980 to 61.66 mg per person in 2011.¹ Along with this expansion in opioid-prescribing practice, there have been corresponding increases in opioid-related abuse and death.² Long-term opioid therapy does remain controversial for a number of reasons. There is limited availability of scientific evidence in the setting of chronic noncancer pain to guide pain management. In addition, opioid therapy is vulnerable to misuse and/or abuse given its psychotropic and potentially addictive effects.

Despite these legitimate concerns, pain management experts recommend that patients suffering from chronic nonmalignant pain should not be denied opioid therapy, despite hesitation surrounding their long-term use (related to adverse effects, long-term tolerance, and the potential for misuse and/or addiction).^{1,3,4}

The decision to initiate long-term opioid therapy must be carefully weighed. After a comprehensive medical history and physical examination, physicians can clearly establish that nonopioid therapy has failed. Informed consent procedures should include a discussion of treatment goals, potential risks, and adverse effects.⁴ It is also important to remind patients to lock their medications to prevent drug theft and diversion.

Many practitioners have developed “opioid contracts” to facilitate informed consent and mandatory follow-up. The value of these treatment agreements, however, has yet to be demonstrated by high-quality evidence. Controversy surrounds their use, particularly because of the impact of the substantial legal ramifications after inappropriate prescription of opioid analgesics.⁴ When possible, it is optimal to involve a single clinician and pharmacy for patient safety and monitoring. In addition, individualized treatment strategies are often necessary. To adequately treat pain and minimize adverse side effects, the counsel of a

specialist with expertise in pain management may be required.⁵

SELECTING OPTIMAL AGENTS AND DOSING SCHEDULES

Key points

- In general, for the management of chronic pain, pure μ -opioid agonists are chosen
- Chronic pain treatment with opioids is largely based on the intensity of pain, patients' previous and current analgesic regimens, and comorbid medical illnesses

Opioid agonists bind to and activate endogenous μ receptors in the brainstem to produce analgesia. Opioid analgesic effects are complex, and a given opioid may function with different potencies as an agonist, partial agonist, or antagonist at >1 receptor class or subtype. It is therefore unsurprising that these agents are capable of diverse pharmacologic effects.⁶ The American Pain Society and American Academy of Pain Medicine outlined recommendations for the management of chronic pain (Table I). Generally, chronic pain treatment should begin with regular administration of shorter-acting opioids (every 4 to 6 hours for most oral agents) until adequate analgesia is achieved. After a short-term initial trial of opioid treatment, patients and clinicians may choose to proceed with longer-term therapy.⁴ Low-dose short-acting agents continue to be recommended in this setting because of the reduced risk of inadvertent overdose.

For treatment of sustained pain, around the clock dosing or transition to a longer-acting opioid is reasonable. Longer-acting formulations permit superior, prolonged relief without rebound pain caused by a rapid fall in plasma opioid concentrations.⁵ Although it remains controversial, they are potentially associated with improved adherence profiles and a decreased potential for abuse. To dose a long-acting opioid, clinicians may first prescribe and titrate short-acting agents. The 24-hour short-acting drug requirement may then be converted to a sustained release preparation to be dosed 2 to 3 times daily around the clock. Conventionally, two-thirds of the daily requirement is prescribed as a long-acting formulation, with doses of immediate-acting drug to be taken on an as-needed basis (calculated as 5-15% of the total daily opioid dose).⁷ Low-risk patients on stable as-needed doses of short-acting agents need not switch to a different regimen if clinically unnecessary.⁴ When patients develop tolerance, they may require an increase dose of opioid to achieve a given analgesic effect. Clinicians may then use the following approaches:

Table I. Common opioid analgesics and typical doses for pain relief^{3,13}

Generic name	Dosing guideline* (PO unless specified)	Duration of analgesia, hours	Comments
Codeine	15-60 mg q4h	3-4	
Oxycodone	5-10 mg q4-6h	3-4	Usually available with acetaminophen or aspirin; sustained release form (OxyContin) available
Morphine [†]	Start 10-15 mg q4h	4-5	Sustained release form (extended release morphine) available; dosed 15-60 mg BID to TID
Hydromorphone	2-4 mg q4-6h	4-5	Shorter-acting than morphine
Levorphanol	2 mg q6-8h	4-5	Longer-acting than morphine sulfate; absorbed well PO
Methadone [†]	5-20 mg q6-8h	4-6	Long half-life; therapy should not be initiated with >40 mg/day; dose escalation should be made no more frequently than every 3 days
Fentanyl [†]	25-100 µg/hr TOP	N/A	72-hour transdermal patch
Tramadol	Start at 50 mg q12-24h	4-6	Mixed opioid/adrenergic mechanism; can increase incrementally up to 400 mg total daily dose

BID, Twice daily; PO, per os; q4h, every 4 hours; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours; q24h, once daily; TID, three times daily; TOP, topically.

*Combination opioid products are offered in a range of available doses, including codeine (15-60 mg codeine/tablet), oxycodone or hydrocodone (2.5-10 mg opioid/tablet), and acetaminophen (325-750 mg/tablet). Clinicians should only prescribe 1 combination product at any given time. Pay close attention to the total daily dose of acetaminophen/nonsteroidal antiinflammatory drug, and avoid prescribing doses of acetaminophen >325 mg/tablet. Patients with renal or liver dysfunction are at high risk for adverse effects. For intravenous opioid dosing, use a weight-based measurement of parenteral morphine (0.1 mg/kg is recommended). This may be delivered as morphine sulfate or converted to a morphine equivalent. Please refer to package insert for guidance on conversion from other opioids.

[†]Use caution when starting long-acting opioid analgesics in patients who are opioid-naïve. Overdose is a risk.

increase the current opioid dose (typically 10-20%), switch to a different opioid, and/or add a nonopioid to the current regimen.⁵

Certain additional agents, including tramadol and tapentadol, are also sometimes selected for the treatment of mild to moderate pain.^{8,9} Tramadol is a mechanistically unique codeine analog that is both a μ -opioid agonist and a serotonin and norepinephrine reuptake inhibitor. Its analgesic efficacy is established across a range of conditions, and it is associated with less respiratory depression than equianalgesic doses of codeine. Tramadol may represent a useful alternative to conventional opioids in patients with cardiopulmonary compromise, such as the elderly, smokers, and obese patients.^{10,11} In addition, tramadol permits a nonsteroidal antiinflammatory drug (NSAID)-sparing effect that can be helpful when patients otherwise have contraindications to NSAID use.¹² Conversely, tramadol potentially offers broader-spectrum analgesia because of its availability as a fixed-dose combination with acetaminophen. It can therefore yield improved convenience, adherence, and an improved ratio of efficacy to adverse effects.⁸ Of note, tramadol and tapentadol are not to be used concurrently with agents that enhance monoamine activity or lower the seizure threshold.

Low-potency agents, such as codeine, are 10% to 25% as potent as morphine sulfate, and commonly chosen for mild to moderate pain exceeding the

analgesic capacity of nonopioid therapy. Many of these agents are formulated in combination with acetaminophen, the maximum dosage of which often limits dose escalation.⁹ Among higher-potency agents, morphine and oxycodone are widely chosen agents used for all types of pain, particularly that of moderate to severe intensity. Morphine is available in both short- and long-acting formulations for delivery via a variety of routes. Hydromorphone can be a useful agent for severe pain; its potency is 6 to 7 times that of morphine. This is often used as a short-acting “rescue” agent for patients who are taking longer-acting opioid preparations.⁹ Finally, fentanyl is a semisynthetic short-acting opioid that is available in many formulations; its analgesic potency is approximately 75 times that of morphine.¹³ Generally, the use of fentanyl is often best guided by a consultant familiar with its clinical use.

Effective chronic pain management with opioid medications includes close attention to minimizing side effects, which include sedation, nausea, constipation, cognitive impairment, urinary retention, respiratory depression, pruritus, and sexual dysfunction.⁹ Constipation is an almost inevitable side effect of chronic opioid therapy and should be anticipated with prescription of a prevention regimen (ie, using docusate, bisacodyl, or senna concentrate and a hyperosmotic agent, such as milk of magnesia). For a subset of patients, a reduction in opioid dosage

(and/or use of antiemetics and laxatives) may be sufficient. Intolerable adverse effects can, however, merit discontinuation of long-term therapy. Overall, there is no clear evidence to suggest which opioid formulation is superior for initial management.¹⁴ If patients are unable to achieve a desirable outcome using the first opioid agent or dose, then dose escalation and opioid rotation are important to consider.

Regarding combination drug therapy, there is unfortunately a lack of information on the choice of pain syndrome-specific drug combinations.^{15,16} The rationale for combination therapy is based on 2 general approaches. The first approach recognizes that it is possible to obtain a desired pharmacologic effect with 2 compounds. This dose-sparing technique can minimize potential side effects and enhance therapeutic efficacy of either individual agent.¹⁷ The second approach is that side effects may be minimized when a given drug combination contains 1 drug that counteracts the effect of another drug in the regimen, such as diclofenac and misoprostol.¹⁶

Currently, >50 opioid combination products are available in various tablet strengths and liquids. These agents are most often initially selected for treatment of moderate pain with episodic features, on an as-needed basis. Acetaminophen, aspirin, and/or ibuprofen are often combined with an opioid in these formulations. Commonly used opioid components include codeine, hydrocodone, oxycodone, or propoxyphene. Caffeine and/or a barbiturate may also be present. In terms of intrinsic analgesic potency, oxycodone and hydrocodone are the most potent and roughly equianalgesic to each other. Codeine is of intermediate potency, and propoxyphene is the least potent. In 2010, the United States Food and Drug Administration (FDA) recommended against the use of propoxyphene and it was voluntarily withdrawn from the market primarily because of cardiotoxicity and an increased risk of seizures.^{18,19} Patients may experience classic opioid-related side effects that limit tolerability of combination formulations, and these agents carry a similar risk of abuse and overdose as noncombination agents. In all of these combination products, the acetaminophen or NSAID is the dose-limiting property. Acetaminophen dosages range from 325 to 750 mg. Of note, in January 2014, the FDA issued a recommendation that health care professionals discontinue prescribing combination products containing >325 mg of acetaminophen per tablet. Plans are ultimately in process to expedite the removal of high-dose acetaminophen combination products from the market. Clinicians should pay

close attention to the total daily dose to limit hepatotoxicity and/or inadvertent overdose.^{20,21}

DOSE TITRATION AND OPIOID ROTATION

Key points

- Patients' functional status, psychological condition, and pain level may fluctuate after initiation of opioid therapy, often requiring dose titration
- Opioid rotation may improve efficacy and reduce both adverse effects and the requirement for dose escalation

Individualized opioid dosing is generally required to achieve a satisfactory balance between pain control and adverse effects. Incremental dose adjustment can assist in determining the lowest effective opioid dose suitable for maintenance therapy. Generally, the daily dose may be increased by 25% to 100%, with a frequency of once every 5 half-lives or longer for a given agent. Larger incremental dose escalation is acceptable (such as up to 100% increase in the daily dose) for continued severe pain if necessary for acceptable analgesia.²² Gradual dose escalation is required to minimize potential toxicity, to manifest full dosage effect, and to allow sufficient time for patients to develop tolerance to adverse effects. This is particularly important to consider in elderly and opioid-naïve patients. Repeated dose escalation for complete pain relief, however, may represent an unrealistic goal in the treatment of chronic pain. If pain management exceeds one's level of comfort or expertise, then it may also be prudent to refer patients for specialized pain management guidance.

A particular agent may prove to be inadequate for pain management, potentially because of the accumulation of toxic/active metabolites, altered pain pathophysiology, individual pharmacogenetic variation, or drug interactions. Opioid rotation may be an effective strategy in this setting, which refers to the practice of using a different opioid agonist when patients fail to achieve goals of therapy with an initial agent. Indications for opioid rotation include intolerable adverse effects encountered during dose titration, poor analgesic efficacy despite titration, drug interactions, a change in clinical status, and financial considerations.²³ The phenomenon of incomplete cross-tolerance has been noted among different opiate receptors, reflecting the numerous genetic polymorphisms and resulting diversity in endogenous opiate receptors.⁴ As such, failure or intolerance to 1 opioid cannot necessarily predict the response to another agent; this provides the rationale for opioid rotation.

Table II. Characteristics of opioid withdrawal and patient nonadherence^{5,23}

Signs	Symptoms
Craving for opioids	Pupillary dilation
Restlessness, irritability	Sweating
Increased sensitivity to pain	Piloerection
Nausea, cramps, or myalgia	Vomiting, diarrhea
Dysphoric mood	Tachycardia, hypertension
Insomnia	Yawning
Anxiety	Fever
Typical features of nonadherence to therapy	
Unexpected results on toxicology screening	
Frequent requests for dosage increases	
Concurrent use of nonprescribed psychoactive substances	
Failure to follow dosage schedule	
Failure to adhere to concurrently recommended treatments	
Frequently reported loss of prescriptions or medications	
Frequent visits to the emergency room for opioid therapy	
Missed follow-up visits	
Prescriptions obtained from a second provider or nonmedical sources	
Theft of drugs or prescription medications from others	
Prescription forgery	
Tampering with prescription	

For opioid rotation, in anticipation of lower patient tolerance to a different agent, the second drug should be started at half the dose equivalent of the first. In a step-wise rotation, the old opioid dose may be reduced by 25% to 50% when the new agent is started. This may be preferable when switching large doses of opioids. A second approach is a single-step method, whereby the old agent would be stopped and the new opioid started in an equianalgesic dose. Pain may worsen if the new agent has delayed peak analgesic effect.⁴ The method by which to undertake opioid rotation is best left to the clinical judgment of the provider and the circumstances warranting opioid rotation. Opioid rotation is complex—particularly in patients who are receiving higher doses—and input from a consultant should be sought.

It is also important for patients and providers to understand the phenomena of physical dependence and tolerance. These normal physiologic consequences of prolonged opiate therapy are distinct from opioid addiction. Physical dependence to opioids is characterized by a physiologic state in which a withdrawal syndrome results after abrupt opioid dose reduction (Table II).²⁴ Although unpleasant, opioid withdrawal is not inherently life-threatening. Its duration and intensity is variable and related to the clearance of the specific opioid.²⁵

Treatment of acute withdrawal typically involves return to a prescription opioid medication. A 10% weekly dose taper is usually well-tolerated with minimal physiologic effects of withdrawal.²³ Another potential approach to treat opioid withdrawal involves the use of clonidine, but its use is often limited by patient tolerability. Withdrawal can ultimately be minimized with appropriate dosing regimens or the use of long-acting agents.

Addiction, in contrast to physical dependence, features impaired control, compulsive and continued use despite harm, and drug craving. A related phenomenon, opioid tolerance, can be readily managed and is manifested by a need for increased opioid dosing to produce a given analgesic effect. Patients often develop tolerance to both the analgesic and the unwanted side effects of opioids. By selecting the lowest effective opioid dose necessary, clinicians can reduce the likelihood of tolerance.

THERAPEUTIC MONITORING AND MANAGEMENT OF TREATMENT FAILURE

Key points

- Periodic review and careful monitoring for signs of opioid misuse, including toxicologic screening, are required for patients on chronic opioid therapy
- Treatment failure or nonadherence may necessitate discontinuation of opioid therapy

For chronic opioid therapeutic monitoring, it is important to routinely reassess the efficacy of pain management and discuss whether initial treatment goals are being met (Table III). Monitoring entails documentation of pain intensity, functional status, therapeutic progress, adverse effects, and medication adherence. Periodic urine drug screens are also recommended for aberrant drug-related behavior or risk factors.²³ For low-risk patients, monitoring at least every 3 to 6 months may be sufficient. More frequent follow-up may be used as needed. Studies suggest an approximately 3% prevalence of abuse/dependence among chronic opioid users, associated with factors including younger age, mental health disorders, and previous substance abuse.²⁶ National statistics on prescription drug abuse shed light on the significance of this issue. In the United States, 52 million individuals ≥12 years of age have used prescription drugs nonmedically in their lifetime. Statistics in 2010 showed that 5.1 million individuals abused prescription pain medication.²⁷ For suspected aberrant drug-related behavior, tapering and discontinuation of opioid therapy is often indicated.

Table III. Suggested protocol for opioid therapy and monitoring²³

A. Decision to initiate therapy		
Confirm diagnosis and failure of nonopioid and nonmedical treatments		
Ensure that balance of risk and benefit favors treatment		
Establish treatment goals, request written consent and/or contract when necessary		
B. Dose adjustment: up to 8 weeks		
Start therapy at low standard dose, increasing as tolerated to achieve acceptable analgesia		
Discontinue opioid if satisfactory analgesia is not achieved or adverse effects are intolerable		
C. Maintenance of stable, moderate dose		
Monthly refills		
Require in-person prescription pick-up		
Assess and document patient's pain score and side effects of opioid treatment		
Treat side effects		
Refer patient for comprehensive follow-up if indicated		
D. Outcomes		
Successful treatment	Dose escalation	Treatment failure
Treatment achieves ≥ 1 of the following:	Exclude or identify disease escalation	Includes ≥ 1 of the following criteria:
Pain relief that improves well-being	Hospitalize if necessary	Failure to achieve success
Progress toward goals	Repeat dose adjustment	Evidence of addiction
Improved function	Aim to reach new, stable, moderate dose	Noncompliance
Improved quality of life		Wean and discontinue therapy
Continue stable dose and follow-up	Dose escalation failure	
	Opioid rotation: switch agent and start at lower dose	
	OR	
	Wean and discontinue therapy: restart opioid after period of abstinence, if necessary	

In general, it is advisable to avoid complying with patient demands for increased analgesia if treatment goals are not being met. If attempts to limit the opioid dose escalation fail, then reassessment of pain management must occur. Careful weaning and discontinuation of opioids over several months may be necessary to truly assess the need for ongoing opioid therapy. Some patients' coping mechanisms and pain intensity in turn improve. For those patients with persistent pain off of opioids, therapy may be reinitiated and often requires lower doses than initially prescribed.⁴ Aberrant or drug-seeking behavior complicates opioid management (Table III). For a subset of patients, this may represent inadequacy of analgesia. Pending optimal treatment, this behavior will revert to normal. It is more concerning when noncompliance reflects abusive behavior. This should prompt closer monitoring and tighter medication administration, or discontinuation of opioids altogether.

Several factors lead to taper and cessation of therapy beyond aberrant opioid use—namely, failure to progress towards therapeutic goals and/or intolerable adverse effects. A 10% weekly dose reduction is generally safe and tolerable. A more rapid weaning rate may be used in high-dose therapy and slowed at the morphine equivalent of 60 to 80 mg per day.²³ It remains vital that patients receive close follow-up care, including ongoing dermatologic treatment, appropriate psychiatric care, and pain management with nonopioid analgesics.

In conclusion, whenever relevant, it is essential that clinicians address pain during a comprehensive assessment in dermatology. Part I of this 2-part continuing medical education article discussed the initial assessment of pain, with guidelines for management using nonopioid analgesics. For severe pain, therapeutic escalation and/or incorporation of opioid analgesia may be necessary for symptom relief. An algorithmic approach to these recommendations is presented in Fig 1. As outlined in this

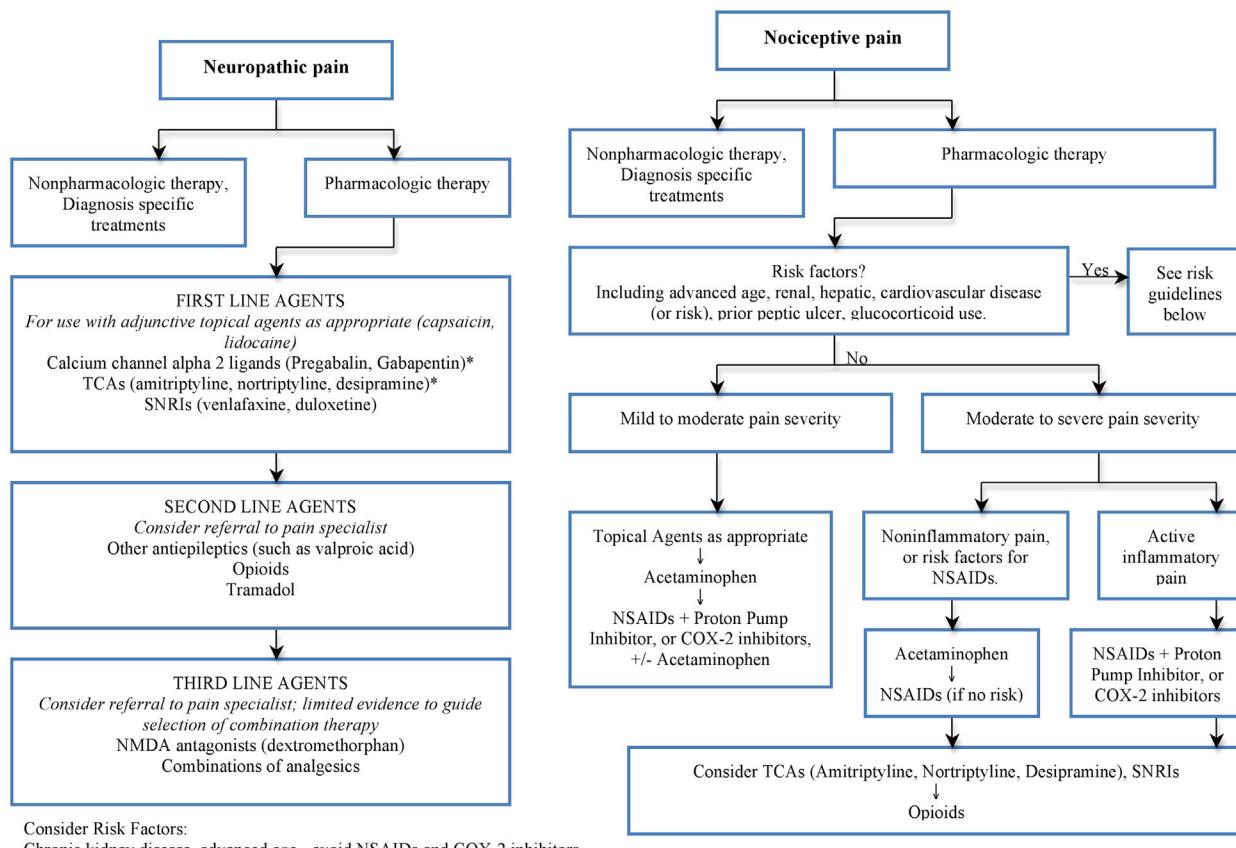


Fig 1. Summary algorithm for the treatment of chronic nociceptive and neuropathic pain.

article, complex issues arise in chronic pain management and necessitate frequent therapeutic monitoring and/or dose escalation. In particularly challenging situations, referral to a specialist in pain or addiction may best address a patient's ongoing needs. Awareness of the burden and management of chronic pain is essential for a sound therapeutic alliance. Through the appropriate treatment of both pain and primary cutaneous disease, dermatologists can ultimately provide effective support, counseling, and therapeutic strategies to improve patients' quality of life.

REFERENCES

1. Cheung CW, Qiu Q, Choi SW, et al. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. *Pain Physician*. 2014;17:401-414.
2. Kissin I. Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety? *J Pain Res*. 2013;6:513-529.
3. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372-380.
4. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943-1953.
5. Rathmell JP, Fields HL. Pain: pathophysiology and management. In: Fauci A, Longo DL, Kasper DL, et al, eds. *Harrison's principles of internal medicine*. New York (NY): McGraw-Hill; 2012.
6. Schumacher MA, Basbaum AI, Way WL. Opioid analgesics and antagonists. In: Katzung BG, Masters SB, Trevor AJ, eds. *Basic and clinical pharmacology*. New York (NY): McGraw-Hill; 2012.
7. American Pain Society. *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*. Glenview, IL: American Pain Society; 2003.
8. Pergolizzi JV, van de Laar M, Langford R, et al. Tramadol/paracetamol fixed-dose combination in the treatment of moderate to severe pain. *J Pain Res*. 2012;5:327-346.
9. Reddy SK, Lopez G, Elsayem A. Pain Management and Symptom Control. In: Kantarjian HM, Wolff RA, Koller CA, eds. *The MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2011.
10. Sullivan MD, Robinson JP. Antidepressant and anticonvulsant medication for chronic pain. *Phys Med Rehabil Clin N Am*. 2006;17:381-400. vi-vii.
11. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet*. 2011;377:2226-2235.
12. Schug SA. The role of tramadol in current treatment strategies for musculoskeletal pain. *Ther Clin Risk Manag*. 2007;3:717-723.
13. Ripamonti CI. Pain management. *Ann Oncol*. 2012;23(Suppl 10):x294-x301.

14. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. *J Pain Symptom Manage.* 2003;26:1026-1048.
15. Eckhardt K, Ammon S, Hofmann U, Riebe A, Gugeler N, Mikus G. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg.* 2000;91:185-191.
16. Mao J, Gold MS, Backonja MM. Combination drug therapy for chronic pain: a call for more clinical studies. *J Pain.* 2011;12:157-166.
17. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med.* 2005;352:1324-1334.
18. Gloth FM. Pain management in older adults: prevention and treatment. *J Am Geriatr Soc.* 2001;49:188-199.
19. Raffa RB, Burmeister JJ, Yuvasheva E, Pergolizzi JV. QTc interval prolongation by d-propoxyphene: what about other analgesics? *Expert Opin Pharmacother.* 2012;13:1397-1409.
20. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician.* 2014;17:E119-E128.
21. Michna E, Duh MS, Korfes C, Dahl JL. Removal of opioid/acetaminophen combination prescription pain medications: assessing the evidence for hepatotoxicity and consequences of removal of these medications. *Pain Med.* 2010;11:369-378.
22. Management of chronic opioid therapy. US Department of Veteran Affairs Website. http://www.healthquality.va.gov/Chronic_Opioid_Therapy_COT.asp. Accessed October 31, 2012.
23. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10:113-130.
24. Adriaensen H, Vissers K, Noorduin H, Meert T. Opioid tolerance and dependence: an inevitable consequence of chronic treatment? *Acta Anaesthesiol Belg.* 2003;54:37-47.
25. O'Brien C. Drug addiction. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* New York: McGraw-Hill; 2012.
26. Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. *Drug Alcohol Depend.* 2010;112:90-98.
27. National Institute on Drug Abuse. *Popping Pills: Prescription Drug Abuse in America.* Bethesda, MD: National Institutes of Health; 2014. Accessed May 1, 2014. <http://www.drugabuse.gov/related-topics/trends-statistics/infographics/popping-pills-prescription-drug-abuse-in-america#1>.

Study designs in dermatology

A review for the clinical dermatologist

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Learning objectives

After completing this learning activity, participants should be able to describe the most common study designs encountered in dermatology, including observational, prospectively controlled, case control, cohort, and randomized control studies and metaanalyses, and recognize the appropriate use of statistical tests and matching in study design.

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A working knowledge of common research study designs and their advantages and disadvantages is necessary for critical reading of the literature by clinicians. However, understanding study designs and related statistical methodologies may be perceived as being complex and difficult to execute. This review aims to provide a practical foundation for basic study designs and to help physicians identify pitfalls that commonly occur in clinical studies and their level of evidence. Topics covered include the pros and cons of observational versus prospectively controlled studies, case-control, cohort, randomized controlled studies, adaptive controlled trials and metaanalyses, and the role of matching in studies. (*J Am Acad Dermatol* 2015;73:721-31.)

Key words: adaptive controlled trials; bias; case-control study; cohort study; cross-sectional study; epidemiology; matching; metaanalysis; observational study; prospectively controlled study; randomized controlled study; retrospective; study design.

INTRODUCTION

Study designs and related statistical methodology are integral parts of dermatology research and publication, bridging clinical and basic science research with clinical dermatology practice. These tools are at the center of analysis, interpretation, and presentation of data and are the cornerstone of evidence-based research in science and all fields of medicine, including dermatology.

Over the past few decades, dermatology research has burgeoned from case series and small-scale clinical trials to include large-scale, randomized,

controlled studies and, in some situations, sophisticated epidemiologic studies. Despite the proliferation of complex studies involving multiple statistical techniques, study design and methodology have not been given much attention in the dermatology literature.

The goal of this review is to provide the reader with a foundation for practical basic study designs and statistical and epidemiologic methodologies and to help physicians identify common pitfalls that are ubiquitous in clinical and basic science dermatology research. In particular, this review is targeted at

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providing a foundation for dermatologists and others involved in the delivery of dermatologic care. Those who regularly read the dermatology literature require a keen ability to critically read manuscripts and to recognize strengths and weaknesses in both study design and the methodologies used, which may ultimately affect the strength of the conclusions set forth in a manuscript.

Study design

Key points

- **Retrospective studies may particularly be complicated by less rigorous planning, poorer data quality, an inability to control for confounding factors, and several potential biases**
- **Cohort studies compare exposed and unexposed subjects in terms of subsequent outcome**
- **Case-control studies compare subjects with and without a particular outcome in terms of preceding exposure**
- **Randomized controlled studies are the standard of single-study designs**
- **Metaanalyses involve the statistical analysis of the combined results of multiple studies and are limited by the quality and heterogeneity of the individual studies included**

The dermatology literature is replete with various study designs, including case reports, case series, cohort studies, case-control studies, and controlled therapeutic trials (Table 1; Fig 1). Factors that influence the choice of study design include availability of time to complete the study, research funding available and type of funding, and how common is the disorder being studied (ie, prevalence/incidence or the number of patients available in the practice or clinic setting and the time to generate the patients), ethical issues, and statistical design.

The findings reported in a case report are limited because they are anecdotal; in general, there is limited evidence and no role for study design or statistics.

Observational versus experimental studies

Key points

- **Experimental studies control subjects' assignment to an exposure or treatment group**
- **The Strengthening the Reporting of Observational studies in Epidemiology guidelines are generally accepted for the proper reporting of observational studies**

Studies can be divided into 2 broad categories: observational and experimental. Observational studies differ from experimental studies in that subjects' assignment to an exposure or treatment group is not controlled in the study. It is not always feasible, cost effective, or ethical to perform an experimental study. Observational studies are often more practical for assessing the effects of a therapy or intervention because they may be less expensive, easier to run, and pose fewer ethical challenges by not deliberately withholding treatment in a placebo group. Observational studies are also commonly used to study associations between various exposures, such as environmental risk factors and disease outcomes.

There are multiple types of observational studies, including cross-sectional, case-control, and cohort studies. These study designs have both common and unique pitfalls that need to be appropriately reported for readers to properly assess the validity, strengths, and weaknesses. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) initiative developed guidelines for the proper reporting of observational studies, including prespecified hypotheses, key elements of the study design and data analysis, essential reporting of participant numbers, and characteristics and interpretation of results.¹

There are multiple types of experimental or interventional studies, including interventional studies without parallel groups and randomized controlled trials (RCTs). Interventional studies without parallel groups are analogous to case series and will not be reviewed. RCTs will be reviewed below.

Retrospective versus prospective studies

Key point

- **Retrospective studies involve data collection before study initiation and are affected by less rigorous planning**

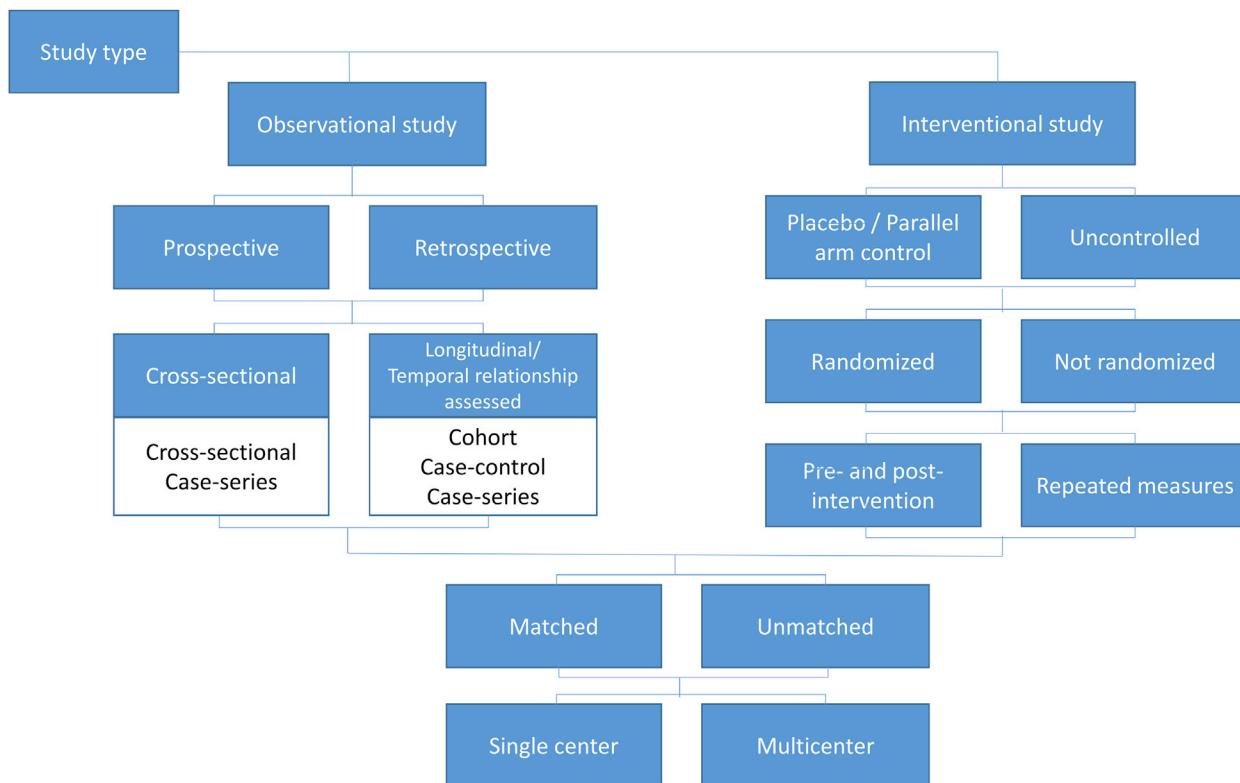
Studies can be further divided into retrospective and prospective studies. These terms refer to whether the data were collected before or after the initiation of the study. Retrospective studies involve retrospective analysis of already collected data, usually from data sources ranging from small, single-site chart and electronic medical record reviews to international epidemiologic databases and comprehensive health management organization cohorts. In prospective studies, data are collected throughout the study period. Of note, the term prospective is also colloquially used to describe longitudinal studies, where patients are followed

Table I. Study designs

Design*	Definition	Level of evidence		Pros	Cons
		USPSTF ¹⁸	JAAD		
Metaanalysis ²⁵	Statistical analysis of the combined results of multiple randomized, well controlled trials	I (highest)	IA (highest)	Ability to qualitatively evaluate multiple studies; increases the numbers of subjects and statistical power; results may be generalized to the multiple cohorts represented by each individual study	Only as good as the individual studies included for analysis; questionable validity of estimates of the effect size for an intervention or association because of inherent differences of included studies
Randomized controlled study ²⁶	Randomized controlled studies compare ≥2 treatment groups, whose members are randomly selected, for a subsequent outcome	I (highest)	IB	Better a priori planning; better quality data; randomization; blinding of subjects and observers when used	Expensive; more time to complete; difficulty enrolling large numbers of subjects; dropout bias; limited generalizability
Controlled trial/quasiexperiment	Controlled trials compare ≥2 treatment groups, whose members are not randomly selected, for a subsequent outcome	II-1	IIA		
Cohort analysis	Cohort studies compare between exposed and unexposed subjects for a subsequent outcome	II-2	III	Practical if exposure is rare; able to show a temporal relationship; able to determine the true incidence of an outcome	Expensive when prospective; more time to complete when prospective; impractical if outcome is rare; difficulty enrolling large number of subjects; dropout bias
Case-control analysis ²⁷⁻²⁹	Case-control studies compare between subjects with and without a particular outcome for a preceding exposure	II-2	III	Inexpensive; less time to complete; practical if outcome is rare	Less rigorous a priori planning; poorer data quality; inability to control for confounding factors; observational bias; selection bias; recall bias;
Case series/single-arm trial	Report of multiple clinical cases or subjects with a finding	II-3	IV (lowest)	Inexpensive	impractical if the exposure is rare; unable to show temporal/causal relationship; unable to determine incidence of an outcome
Case report	Individual report of a clinical case or finding	III (lowest)	IV (lowest)		Anecdotal

JAAD, Journal of the American Academy of Dermatology; USPSTF, United States Preventive Services Task Force.

*References for reviews of a particular study design in dermatology are included where available.

**Fig 1.** Study designs.

repeatedly over time. However, prospective studies do not have to be longitudinal and may involve only a single assessment.

In many prospective studies, there is significant wait time necessary until the outcomes of interest occur. In contrast, there is no wait time for outcomes to occur in retrospective studies. Retrospective studies are relatively inexpensive and require fewer resources because much of the diagnostic work was conducted and paid for before initiation of the study. Retrospective studies may be the only options available for many, if not most, scientists who have minimal or no research funding and are desperately trying to make their contribution.

Because data in retrospective studies are collected before initiation of the study, they are often particularly affected by less rigorous *a priori* (decided upon before the onset of the study) planning, poorer data quality, an inability to control for confounding factors, and several potential biases. Of course, many of these limitations can also occur in prospective studies, but are typically less common with adequate advanced planning of the study. Data from retrospective studies can be analyzed with a myriad of statistical techniques that may yield different results. Without proper *a priori* planning, researchers might be tempted to try multiple approaches, use one that yields the best results,

and ignore the approaches that do not fit with the *a priori* hypothesis. *A priori* hypotheses and which analyses were planned at the onset of the study versus being data-driven or post hoc analyses should be reported for readers to properly assess a study.¹

Retrospective studies may have poorer data quality for difficult to define outcomes, or if the data were not entered in a consistent manner with standardized terminology. For example, atopic dermatitis (AD) can be defined by a variety of criteria, including the Hanifin and Rajka,² United Kingdom Working Party's criteria,^{3,4} or simply intermittent flexural eczema. A multicenter study where each provider uses different criteria may have problems related to bias, heterogeneity, and an inability to pool and interpret results. In addition, control subjects and data pertaining to important confounding variables may be limited or unavailable in retrospective studies if they were not addressed before study onset.

Retrospective studies may suffer from information bias for an exposure or outcome if data were not measured in a standardized manner across all subjects. For example, the frequency of nevi may be measured more carefully and accurately in patients with heavily sun-damaged skin than in those with less evidence of chronic sun exposure.

Table II. Types of bias in research studies

Bias	Definition	How to avoid
Ascertainment or sampling bias	Systematic error introduced by the sampling method; study sample is not representative of the target population	Random sampling; population-based sampling to include all sociodemographic levels; random allocation to an intervention
Attrition or transfer bias	Systematic differences between groups in withdrawals from a study; outcome data are not available; may be caused by treatment failure or disease resolution	Minimize loss to follow-up by offering convenient office hours, personalized patient contact via phone/email, and investigator visits to the patient's home
Confounding	Association between an exposure and outcome is caused by a third variable that is correlated to both	Matching cases and controls by the confounding factor; stratified and multivariate regression analyses
Data-snooping bias	Performing a large number of statistical tests increases the type I error rate; so-called "fishing expedition"	Hypothesis-driven testing rather than data-driven testing; correction for multiple comparisons
Detection bias	Systematic differences between groups in how outcomes are determined	Blinding
Exposure misclassification	Measurement error because of poorly defined exposures or if proxies of exposure are used	Use "criterion standard" assessment and objective tests; correct for differential misclassification between groups
Funding bias	Systematic preference toward performing funded studies; tendency of the research to support the study's sponsor	Investigator-initiated and unfunded research studies
Hawthorne effect	Systematic differences in behavior or response in a subject who knows they are being investigated	Placebo group
Information or measurement bias	Systematic error in measurement of an outcome or exposure	Standardized measurements and instruments and use of multiple data points for improved accuracy
Interviewer or observer bias	Systematic difference between how information is solicited, recorded, or interpreted	Blinding
Lead-time bias	Systematic error because of cases being detected at different stages of disease; early detection does not equal improved survival	Correction for lead-time and length bias (often very challenging)
Nonresponse bias	Some subjects may not participate or respond to questionnaires because of various personal factors	Assess for systematic differences between responders and nonresponders; data interpolation techniques for nonresponders
Outcome misclassification	Measurement error related to poorly defined outcomes or if proxies of outcome are used	Use "criterion standard" assessment and objective tests; correct for differential misclassification between groups
Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	Blinding; giving equal attention and care to all study groups
Procedural bias	Systematic error introduced by the interview or questionnaire being administered with too much pressure on participants	Not imposing time constraints or incentivizing rushing through the questionnaire
Recall bias	Systematic difference between how events or experiences are remembered; better recall of recent or more serious events than those occurring a long time ago; patients suffering from disease are able to recall events more easily than healthy subjects	Confirmation of self-reported exposures and outcomes using the medical record

Continued

Table II. Cont'd

Bias	Definition	How to avoid
Reporting bias	Systematic differences between reported and unreported findings; only significant findings get published	Reporting of negative findings
Selection bias	Systematic differences between baseline characteristics of the groups that are compared	Randomization
Self-improvement effect	Some disorders are self-limiting and may improve independent of an intervention	Placebo group; longitudinal study design that accounts for waxing and waning disease course
Type III error	Solving the wrong problem precisely	Improved communication between investigator and statistician

Biases of prospective versus retrospective studies

There are many types of bias that can occur in the research setting⁵ (Table II). Retrospective studies are often affected by confounding, data-snooping bias, misclassification errors, recall bias, and selection bias. Retrospective studies are commonly cross-sectional and therefore are unable to assess the temporal relationship between exposure and outcome or determine the incidence rates of disease.

Prospective studies are often affected by ascertainment bias because it is costly and time-consuming to assemble a cohort that is representative of the population. Attrition and lead-time bias and self-improvement effects are commonly encountered. Because prospective studies tend to be more expensive, there may also be a funding bias toward studies with commercial interests.

Cross-sectional studies

Key point

- Cross-sectional studies lack temporal information related to exposures and outcomes

Cross-sectional studies provide descriptive data on the prevalence of comorbid exposures and outcomes. They are generally more efficient and cheaper to conduct than other study designs because only a single observation is needed per subject. The strongest limitations of cross-sectional studies are the lack of temporal information related to exposures and outcomes, resulting in an inability to determine the directionality of an association or the incidence of a particular outcome.

Case-control studies

Key point

- Case-control studies select subjects based on their outcome status and retrospectively assess their exposures

In contrast with cross-sectional studies, case-control and cohort studies include information about the temporal relationship between the exposure and outcome. Case-control studies are observational studies that involve the selection of a group of “cases” (having the outcome of interest; eg, disease) and an appropriate group of “controls” (eg, disease-free individuals). The cases and controls are then compared in terms of preceding exposure to ≥ 1 risk factor(s). For example, in a case-control study of whether obesity is associated with childhood AD, cases and controls were defined as children diagnosed and undiagnosed with AD, respectively.⁶ The case and control groups were then compared in terms of prevalence of obesity (ie, the exposure of interest). In general, subjects are selected for the case group of a case-control study based on a single disease. By definition, case-control studies are retrospective—the outcome is already known at the time of enrollment.

The effect sizes for an association between an exposure and outcome in a case-control study are typically reported using odds and odd ratios (ORs). Odds are equal to the probability of the outcome happening divided by the probability of the outcome not happening. An OR is the odds of an outcome occurring in the exposed group divided by the odds in the control group. OR is a relative measure and cannot be used to assess absolute risk or incidence of disease. For example, in a case-control study of US adults with melanoma and age/sex-matched controls that examined whether melanoma was associated with the current use of nonsteroidal antiinflammatory drugs (NSAIDs),⁷ the probability of NSAID use was 66% in the melanoma group and 72% in the control group. These probabilities are equivalent to odds of 1.9 and 2.6, respectively. The OR was 0.73, which means that adults who used NSAIDs had approximately three-quarters the odds of

developing melanoma as those who did not. As illustrated from the study, the OR is a relative measure and does not allow for interpretation of the actual probabilities.

Case-control studies do not require that subjects be followed over time to determine outcome status, and are therefore more practical in scenarios with rare outcomes. However, they are inefficient if the exposure is rare. For example, a case-control study of cigarette smoking as a cause of skin cancer is reasonable given that smoking is still fairly common, but less so for rare exposures (eg, arsenic). Case-control studies involving surveys and patient recollection of previous exposures may also be hindered by recall bias, where patients with a particular disease outcome may be more likely to recall certain exposures or risk factors than controls. For example, people with skin cancer may be more likely to over-report sun exposure.

Cohort studies

Key point

- Cohort studies select subjects based on their exposure status and assess their outcomes

Cohort studies involve the selection of a group of subjects with the exposure of interest along with other less exposed or unexposed groups. These groups are then compared in terms of some outcome of interest. Cohort studies are commonly prospective, but they can also be conducted retrospectively. For example, in a retrospective cohort study⁸ of chickenpox as a protective factor (ie, the exposure of interest) against production of serum immunoglobulin E and allergic sensitization (ie, the outcome of interest), the exposed group consisted of children with wild-type chickenpox infection in the first 8 years of life and the unexposed group consisted of children who were both vaccinated for varicella and did not develop chickenpox. The exposed and unexposed groups were then compared for subsequently elevated immunoglobulin E levels and allergic sensitization, which were the outcomes of interest.

Cohort design requires that subjects be followed over a period of time from exposure to outcome. They allow for better demonstration of a temporal/causal relationship, determination of the true incidence of an outcome, and are practical in scenarios with rare exposure but are impractical when the outcome is rare. The cons of cohort studies include the requirement of a large number of subjects, inconsistent length of follow-up because of attrition, or variable time of entry into the study. They are also prone to detection and/or differential

misclassification biases, where patients with a harmful exposure may be more commonly and/or accurately diagnosed with an outcome than those without the exposure, respectively. For example, previous studies found that patients with AD,^{9,10} psoriasis,¹¹ and even positive patch tests¹² are more likely to develop nonmelanoma skin cancer. However, such patients are more engaged in skin examinations by dermatologists and therefore more likely to be correctly diagnosed than patients without inflammatory skin disease. Finally, there may be a dropout bias where subjects may develop the outcome of interest but it is not detected because of a loss to follow-up.

Randomized controlled studies

Key points

- Randomized controlled studies are the criterion standard of interventional studies
- The Consolidated Standards of Reporting Trials guidelines are generally accepted for the proper reporting of randomized controlled trials

RCTs are considered the standard of single-study designs because they are prospective (making data collection more reliable), use randomization of subjects to study arms (ensuring their equality in respects other than treatment), and can be executed with exquisite control over inclusion and exclusion criteria. This study design is typically used for investigations of novel therapeutic drugs. There may be multiple experimental arms representing different treatments or doses. The control arm may have subjects with placebo, the vector for the experimental drug, or the current standard of care. The cons of RCTs include cost, length of study, and difficulty enrolling sufficient numbers of patients; in addition, ethical considerations may prohibit them, and there is often limited generalizability given the rigorous inclusion and exclusion criteria.

RCTs have many unique sources of bias and specific methodologies to address these potential biases, including random sequence generation and allocation concealment to address selection bias, blinding to address performance and detection bias, maximize complete outcome data to counteract attrition bias, and complete reporting even of negative results to counteract reporting bias. For example, a randomized, double-blind, placebo-controlled, parallel group study found that *Ginkgo biloba* tablets 3 times per day resulted in the significant improvement of vitiligo compared with placebo.¹³ However, a recent metaanalysis found

that this study did not document adequate sequence generation or blinding of the clinician/assessor, which raises questions about a potential major bias.¹⁴

The Consolidated Standards of Reporting Trials (CONSORT) statement and its various extensions developed guidelines for the proper reporting of randomized parallel group trials in manuscripts and abstracts.¹⁵ These guidelines include specific reporting about the objectives, design, participants with characteristic flow diagram, interventions, outcomes, sample size, randomization, blinding, statistics, results, and discussion. The CONSORT guidelines can also be used in part for interventional studies without parallel groups. The discerning reader of RCTs should be alert for these issues, because insufficient documentation of these methods may suggest biased results.

Adaptive controlled trials

Adaptive controlled trials (ACTs) are a relatively new type of clinical trial that starts as other RCTs would but allows for repeated adaptation of initial methodology based on patients already accrued and early results. In RCTs, interim analyses are often performed to identify issues related to safety and efficacy that might prompt premature termination of the study. ACTs capitalize on the interim analyses to modify anything from the randomization approach, target population, sample size, and medication dosing and frequency without having to create a new study. ACTs have been used in dermatology^{16,17} and will likely become more common over time.

Metaanalyses

Key points

- Metaanalyses are considered the highest level of evidence, but are only as good as the individual studies included for analysis
- Metaanalyses should be limited to randomized, well controlled trials wherever possible

Metaanalyses involve the statistical analysis of the combined results of multiple studies. The benefits of metaanalyses include the ability to qualitatively evaluate multiple studies, increase the numbers of subjects and statistical power as the sum of multiple smaller studies, and the results may be generalized to the multiple cohorts represented by each individual study. However, metaanalyses are only as good as the individual studies included for analysis. Inclusion of case series and uncontrolled and retrospective studies is accompanied by all the biases contained therein. Metaanalyses should be limited to randomized, well controlled trials wherever possible

and where the results of included studies are considered to have the highest level of evidence.¹⁸ Finally, there may be questionable validity of estimates of the effect size for an intervention or association because of the inherent differences of included studies.

Metaanalyses require thoughtful analysis of the quality and heterogeneity of the included studies. The most common guidelines used for metaanalysis reporting are the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁹ and the Cochrane Handbook for Systematic Reviews of Interventions,²⁰ both of which address best practices for the reporting and assessment of bias. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group²¹ developed a grading system for the quality of evidence and strengths of recommendations, including study design, imprecision, inconsistency, and indirectness of study results. In addition, the Newcastle-Ottawa 9-point Scale for Assessing the Quality of Nonrandomized Studies in Meta-Analysis is also was used to assess observational study quality.²² There are many issues that affect the results of a metaanalysis, including the search and selection criteria for studies, data collection, assessing risk of bias, data analysis and synthesis, reporting bias, limitations, and funding sources. The discerning reader of systematic reviews and metaanalyses should be alert for sufficient documentation of these issues.

Scientific level of evidence

Key point

- Metaanalyses and randomized controlled trials are considered to have the highest level of scientific evidence

After a careful review of the aforementioned study designs and some of their inherent limitations and biases, it is apparent that not all studies provide the same level of evidence to support an association. Well-designed RCTs prospectively control for issues of randomization, blinding, standardized measures, and outcomes, and have improved follow-up and more complete data. They provide the highest level of evidence for a single study (level IA). Metaanalyses can go even further by including multiple high-quality studies and determining aggregate effects across a larger and perhaps more diverse cohort. They also provide level IA evidence, and are regarded as providing an even higher level of evidence than RCTs by the *Journal of the American Academy of Dermatology*.²³ Other study designs are

deemed inferior and provide lower levels of evidence ([Table I](#)).

Confounding factors

Key points

- **Confounding factors are correlated to both the exposure and outcome of interest in a research study**
- **Confounding may cause spurious results and should be addressed in all studies**

Confounding factors are correlated to both the exposure and outcome of interest in a research study. Identifying potentially confounding factors is necessary for all study designs, is typically challenging, and requires careful a priori evaluation of all demographic and clinical factors that may be risk factors for a disorder, affect response to therapy, et cetera. Once identified, there are several strategies for how to address confounding variables, including controlling for such variables in multivariate statistical models and matching in the study design.

The simplest approach is to control for confounding factors in the statistical models, including analysis of covariance and multivariate regression models. These approaches account for the effects of the confounding factor when examining the association between the outcome and predictor variable(s). When an association is caused by a confounding variable, inclusion of that confounding variable into multivariate models should render the association insignificant.

Matching in study designs

Key points

- **Matching involves the selection of a control group that is the same as the case group with respect to a certain factor**
- **Matching can be performed for potentially confounding variables**

Matching is another strategy that can be used to counteract the effects of confounding. Matching involves the selection of a control (eg, case-control study) or unexposed group (eg, cohort study) that is the same as the case or exposed group with respect to a certain factor, such as age or sex. For example, in a study of the protective role of chickenpox infection against developing AD, age was a confounding factor.²⁴ Age is an important risk factor for developing AD; AD is more common in young children and less common in adolescents and adults. Moreover, age is an important risk factor for chickenpox infection; chickenpox was more common in children before vaccination and most people had positive antibodies to varicella by early

adulthood. Given that increasing age is associated with increased chickenpox infection and less AD, it would be difficult to interpret any association between chickenpox infection and decreased AD. Because age is a confounding factor, it was chosen as a factor on which to match controls to cases.²⁴ Selecting cases and controls of the same age minimizes the confounding effect of age.

Matching is a common strategy in studies that incorporate a control group, such as unexposed subjects in a cohort study, disease-free controls in a case-control study, placebo controls in a therapeutic trial, or untreated experimental controls. Unwanted differences among study arms can result in significant bias and spurious results. A scenario demonstrating such bias can be found in a theoretical therapeutic trial of a novel antiaging cream where the placebo control group is, on average, 30 years older than the treatment group. It would be difficult to make meaningful conclusions from such a study. Randomized trials occasionally use matching, if the size of the study makes plausible the idea that simple randomization could fail; for instance, if only 5 men and 5 women are randomized to 2 study arms, it is not unlikely that nearly all the men will end up in the same group.

Several matching strategies exist, including individual subject matching or frequency matching (both groups have the same mean and standard deviation for age²⁵). However, matching is performed at the expense of requiring more subjects in order to find a subject that matches the designated criteria, thereby prolonging study times for recruitment. Commonly used factors for matching in clinical studies can be found in [Table III](#).

The matching factor must be included in the statistical analysis, and should always be included as a predictor in models with analysis of covariance and regression. The discerning reader and reviewer should be alert for this issue, because not including the matching factor in the model would result in biased statistics. However, matching can be too much of a good thing. Matching on nonconfounding factors or on multiple factors may result in the problem of overmatching, thereby introducing unnecessary bias into the statistical model.²⁵ In many situations, it may be a better strategy to simply control for covariates using regression models than to use matching.

Association versus causation

Key point

- **Associations between variables suggest a relationship, but are not equivalent to causation**

Table III. Common factors used for matching in clinical and epidemiologic studies

Demographics (age and sex)
Race/ethnicity (self-reported or from a genetic profile)
Socioeconomic status (household income, employment status, and insurance status)
Region (neighborhood, ZIP code, city, and state)
Medical history (diagnosis of related disorder)
Physical characteristics (Fitzpatrick skin type, weight, and body mass index)

There is often confusion between about association and causation. Significant associations between an exposure and an outcome in an observational study suggest a relationship between them. However, the relationship may not be causal, because there might be other factors underlying the relationship. Austin Bradford Hill, a renowned British epidemiologist, argued that there are no “hard and fast rules of evidence” for causation. He suggested several factors for consideration of causation, including the following: (1) consistency of the association (ie, reproducibility); (2) strength of the association, where a stronger response is more likely to be causal; (3) biologic gradient, such as a dose-response relationship; (4) specificity of the association (ie, the exposure is associated with a specific definable outcome); (5) the exposure must precede the outcome; (6) coherence (ie, consistency with preexisting scientific knowledge); and (7) biologic plausibility.²⁶ It is important to recognize that the results of many observational studies are insufficient to establish causality and to factor the aforementioned principles into the evaluation of any study.

CONCLUSIONS

Results of research studies can be difficult to interpret because there are many factors that contribute to the appropriate design. It is also important to recognize that there are a number of limitations inherent to different study designs, especially observational studies. Nevertheless, observational studies are here to stay and will continue to become more prevalent because they are inexpensive and easy to perform. Rigorous a priori planning and fixed techniques should be used in observational studies as in controlled prospective studies. It is imperative that our dermatology literature use the highest standards in the peer review process with a greater focus on study design and methodologies.

REFERENCES

- von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370:1453-1457.
- Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh).* 1980;92:44-47.
- Williams HC, Burney PG, Hay RJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol.* 1994;131:383-396.
- De D, Kanwar AJ, Handa S. Comparative efficacy of Hanifin and Rajka's criteria and the UK working party's diagnostic criteria in diagnosis of atopic dermatitis in a hospital setting in North India. *J Eur Acad Dermatol Venereol.* 2006;20:853-859.
- Barzilai DA, Freiman A, Dellavalle RP, Weinstock MA, Mostow EN. Dermatoepidemiology. *J Am Acad Dermatol.* 2005;52:559-573.
- Silverberg JL, Kleiman E, Lev-Tov H, et al. Association between obesity and atopic dermatitis in childhood: a case-control study. *J Allergy Clin Immunol.* 2011;127:1180-1186.e1.
- Curiel-Lewandrowski C, Nijsten T, Gomez ML, Hollestein LM, Atkins MB, Stern RS. Long-term use of nonsteroidal anti-inflammatory drugs decreases the risk of cutaneous melanoma: results of a United States case-control study. *J Invest Dermatol.* 2011;131:1460-1468.
- Silverberg JL, Kleiman E, Silverberg NB, Durkin HG, Joks R, Smith-Norowitz TA. Chickenpox in childhood is associated with decreased atopic disorders, IgE, allergic sensitization, and leukocyte subsets. *Pediatr Allergy Immunol.* 2012;23:50-58.
- Jensen AO, Svaerke C, Kormendine Farkas D, Olesen AB, Kragballe K, Sorensen HT. Atopic dermatitis and risk of skin cancer: a Danish nationwide cohort study (1977-2006). *Am J Clin Dermatol.* 2012;13:29-36.
- Arana A, Wentworth CE, Fernandez-Vidaurre C, Schlienger RG, Conde E, Arellano FM. Incidence of cancer in the general population and in patients with or without atopic dermatitis in the U.K. *Br J Dermatol.* 2010;163:1036-1043.
- Pouplard C, Brenaut E, Horreau C, et al. Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. *J Eur Acad Dermatol Venereol.* 2013;27(suppl 3):36-46.
- Sigurgeirsson B. Skin disease and malignancy. An epidemiological study. *Acta Derm Venereol Suppl (Stockh).* 1992;178:1-110.
- Parsad D, Pandhi R, Juneja A. Effectiveness of oral *Ginkgo biloba* in treating limited, slowly spreading vitiligo. *Clin Exp Dermatol.* 2003;28:285-287.
- Whitton ME, Pinart M, Batchelor J, Lushey C, Leonardi-Bee J, Gonzalez U. Interventions for vitiligo. *Cochrane Database Syst Rev.* 2010;1:CD003263.
- Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010;63:834-840.
- US National Institutes of Health website. Study to demonstrate the efficacy and safety of propranolol oral solution in infants with proliferating infantile hemangiomas requiring systemic therapy. Available at: <http://clinicaltrials.gov/show/NCT01056341>. Accessed August 14, 2014.
- US National Institutes of Health website. Study of a melanoma vaccine in stage IIb, IIc, and III melanoma patients (MAVIS). Available at: <http://clinicaltrials.gov/show/NCT01546571>. Accessed August 14, 2014.
- US Preventive Services Task Force. *Guide to clinical preventive services report of the U.S. Preventive Services Task Force.* Washington, DC: The Task Force; 1989.

19. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62:1006-1012.
20. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* [Updated March 2011.] The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
21. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-926.
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25:603-605.
23. Journal of the American Academy of Dermatology website. Information for authors. Available at: <http://www.eblue.org/authorinfo>. Accessed July 19, 2012.
24. Silverberg JI, Norowitz KB, Kleiman E, et al. Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: a case-control study. *J Allergy Clin Immunol.* 2010;126:300-305.
25. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology.* Philadelphia: Lippincott Williams & Wilkins; 2008.
26. Hill AB. The environment and disease: association or causation? *Proc Royal Soc Med.* 1965;58:295-300.
27. Heacock H, Rivers J. Assessing scientific data: the case-control study as it applies to dermatology part 1; the case-control method. *J Cutan Med Surg.* 1997;1:151-154.
28. Heacock H, Rivers J. Assessing scientific data: the case-control study as it applies to dermatology part 2; interpreting the results. *J Cutan Med Surg.* 1997;2:35-40.
29. Bigby M. Odds ratios and relative risks. *Arch Dermatol.* 2000;136:770-771.

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Study designs in dermatology

Practical applications of study designs and their statistics in dermatology

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Learning objectives

After completing this learning activity, participants should be able to identify the (in)appropriate use of study designs and statistics in dermatology research, describe the levels of evidence for scientific research, and describe how improved study designs have resolved controversies in dermatology.

Disclosures

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A proper understanding of study designs and related statistical methodology is necessary for clinical dermatologists to critically read scientific literature and incorporate this information into clinical practice. This review focuses on how to identify the appropriate use of study designs and the statistical methodology used therein. Topics covered include population sampling and generalizability, power and sample size calculations, correction for multiple statistical testing, and how to identify the appropriate use of statistics. The impact of improved study designs in previously controversial topics in dermatology will be discussed. (J Am Acad Dermatol 2015;73:733-40.)

Key words: bias; categorical; generalizability; interval-scaled; mean; median; nonparametric; ordinal; standard deviation; standard error of the mean; study design.

INTRODUCTION

A proper understanding of study designs and related statistical methodology is a necessary skill set for the clinical dermatologist. The constant development of cosmeceuticals, novel medications, and procedures demands critical evaluation before incorporating into clinical practice. Dermatologists must be able to recognize the practical limitations of various study designs and critically evaluate the presentation of research data in the dermatology

literature. Part I of this continuing medical education article reviewed the fundamentals of study designs and level of evidence. Part II focuses on how to identify the appropriate use of study designs and the statistical methodology used therein. A number of common pitfalls and misuses of statistics previously identified throughout the medical literature¹⁻³ will be addressed. The impact of improved study designs in previously controversial topics in dermatology will also be discussed.

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POPULATION AND GENERALIZABILITY

Key points

- Research studies aim to form a representative sample of the population of interest
- Study findings are only generalizable to persons represented by the study sample

Generally, it is not possible to study the entire population of interest because of time, cost, and/or lack of resources. In many cases, it makes sense to think of a population as being infinite in size (eg, a population of patients past, present, and future who might be given some treatment). Research studies aim to form a representative sample of the population of interest. If the observed sample is truly representative of the population, we can infer that the findings from the observed study groups can be generalized to the population. Selection bias may occur, where subjects may not be representative of the population of interest. For example, a study of patients from a dermatology clinic at an academic medical center may not be reflective of the general population.

Issues of generalizability (external validity) must be considered when interpreting a research study and developing clinical recommendations. For example, mutations of the filaggrin gene were found to be associated with atopic dermatitis (AD). This association has become widely accepted and is the cornerstone for the hypothesis that barrier disruption is the incipient event for AD. Mutations of the filaggrin gene were originally found in persons of Northern European descent and subsequently confirmed in many Asian subpopulations. However, filaggrin mutations are only found in 27.5% of white patients with AD and in 5.8% of African American patients with AD.⁴ Therefore, the finding of filaggrin mutations in AD, while clearly associated with a subset of AD, may not be generalizable to all populations of AD patients.

Many RCTs set rigorous inclusion and exclusion criteria, thereby assembling a sample of “perfect patients” that may not be generalizable to the entire population with a disease. RCTs are therefore useful for establishing efficacy, whereas other study designs are more useful for establishing effectiveness (ie, how well a treatment works in practice).

POWER AND SAMPLE SIZE CALCULATION

Key points

- A type II error occurs when the null hypothesis is falsely retained
- Statistical power is the probability of not making a type II error

- The more power required, and the lower the significance level, the larger the sample size required
- Power analysis and sample size determination should be documented in all observational and interventional studies that use statistical comparisons between groups

It is important to consider issues of powering and sample size calculations when interpreting the results of a study. It is a fundamental principle that the null hypothesis is rejected with a statistically significant result, but is never proved by a statistically insignificant result.⁵ Rather, insignificant results indicate merely that there is insufficient evidence to reject the null hypothesis. It is of course possible to incorrectly retain a null hypothesis that is actually false; this is known as a type II error. With a type II error, an insignificant finding in the observed study group would then be incorrectly generalized to the whole population.

The probability of retaining a null hypothesis if it is false is called beta. Beta values ≤ 0.2 are commonly deemed acceptable (ie, a 20% chance of missing a real difference among populations). Statistical power is the probability of rejecting a null hypothesis if it is false (ie, it measures the ability of a test to correctly reject a false null hypothesis). As a value, power is equivalent to 1 minus the beta value. If a test has high statistical power, it can be asserted with reasonable confidence that a nonsignificant study finding means that population differences are small or zero. On the other hand, a nonsignificant result for a test with low power allows one no confidence to make such a statement.

A priori sample size determination is typically used for designing a study to plan the number of required participants. Reviewers of RCTs will generally insist that this be done. Sample size and power calculations can be quite complex and are typically based on the primary study outcome and are specific to a particular statistical design. Briefly, information needed in order to conduct sample size calculations generally includes specification of: (1) study design; (2) test type; (3) whether the intent is to establish that populations do or do not differ; (4) significance level; (5) whether any difference must be in one direction or could be in both directions; (6) desired power; (7) estimate of how different the populations actually are; and (8) estimate of the extent of within-arm variability. Post hoc power determination can be performed after the completion of a study in scenarios where a priori sample size calculation was not performed or to determine the power for a secondary study

outcome given the sample size collected. While post hoc power analyses are typically deemed to be of inferior value, they offer an opportunity to provide some estimate of a study's power.

However, power and sample size calculations should not be taken for granted. Recent systematic reviews of RCTs in the disciplines of plastic surgery and rehabilitation medicine found that only 19%⁶ and 57.3%⁷ of studies reported formal power and sample size calculations, respectively. The discerning reader should identify whether power and sample size calculations were performed and interpret with caution those studies that report negative findings without mention of a power analysis. In contrast, the null hypothesis may be confidently rejected based on a significant *P* value, even when the study was insufficiently powered. Nevertheless, small studies have other problems, such as possible spurious results, poor precision of confidence intervals, and a lack of power to detect statistical interaction or perform more advanced statistical models.

CORRECTION FOR MULTIPLE TESTING

Key points

- A type I error occurs when the null hypothesis is falsely rejected
- The probability of making at least 1 type I error increases with the number of tests performed
- Corrections should be made for multiple testing

In order to make inferences from the observed study group, statistical significance testing is performed, which requires both null and alternative hypotheses. The null hypothesis typically states that there is no difference between 2 populations, while the alternative states there is a difference. The decision to reject the null hypothesis is made when the observed *P* value is less than some arbitrarily defined value, known as a significance level. By convention, .05 is used, which means that if the null hypothesis is true, the probability of its being rejected is limited to 5%. On the other hand, if the *P* > .05, then there is insufficient evidence from the observed study to reject the null hypothesis about the populations.

If the null hypothesis of every statistical test conducted is true—that is, that there are no genuine differences among the populations—then the probability of making at least 1 type I error increases with the number of tests performed. For example, pairwise independent comparisons among 3 groups with a significance level of .05 for each test actually

results in a 14.3% chance of making ≥ 1 type I errors. Correction should therefore be made for this "multiple testing" problem. This is indicated in studies that perform numerous statistical tests (eg, exploratory and genetic studies).

There are a variety of approaches for multiple test correction, but these methods are beyond the scope of this review. An example of the differences for some of these approaches is found in Silverberg et al,⁸ a study of the protective role of chickenpox infection in children against development of AD and asthma. There were 10 tests (*P* values) related to different aspects of AD. It was deemed likely that the tests were not independent and that Bonferroni method was too conservative with a significance level of .005, whereas controlling the false-discovery rate using the methods of Benjamini and Hochberg⁹ and Benjamini and Yekutieli¹⁰ yielded different significance levels (.03 and .017, respectively). There is no standard approach to correction for multiple testing, and selection of a method should be done on an individual basis.

Unfortunately, many studies in the medical literature do not address the issue of multiple testing. A recent systematic review of 2 orthopedic journals found that only 15% and 6% of published studies, respectively, performed correction for multiple testing.¹¹ The discerning reader of the dermatology literature should cautiously interpret studies that perform multiple statistical tests without correction for multiple testing, especially borderline significant *P* values (ie, those approaching .05).

A PRIORI VERSUS POST HOC DECISIONS

Key points

- A priori decisions are made before study onset
- Post hoc decisions are made after the study onset
- All studies should document which analyses were decided upon (a priori or post hoc)

All studies, whether prospective or retrospective, should have an a priori analysis plan. Generally, prospective studies standardize exposure and outcome measures and any additional variables to be collected at the onset of the study. In contrast, retrospective studies are commonly affected by data-snooping bias or so-called "fishing expeditions." In a retrospective study, there is almost no limit to how many different combinations of variables can be tested post hoc for significant associations. As the number of tests increases, so does the type I error rate (ie, the risk of rejecting the null hypothesis incorrectly). It is important that authors determine

Table I. Data types and respective statistical tests

Outcome variable type	Predictor variable type	Statistical test
Interval-scaled		
ND	Categorical with 2 groups	t test
ND	Categorical with ≥ 2 groups	Analysis of variance
NND	Categorical with 2 groups	Wilcoxon rank sum test
NND	Categorical with ≥ 2 groups	Kruskal-Wallis
ND	Interval-scaled	Pearson correlation
NND	Ordinal, interval-scaled	Spearman correlation
ND	Categorical, ordinal, or interval-scaled	Linear regression
Ordinal		
NND	Ordinal, interval-scaled	Spearman correlation
NND	Categorical, ordinal	χ^2 or Fisher exact test
NND	Ordinal, interval-scaled	Mantel-Haenszel, Kendall τ
NND	Ordinal, interval-scaled	Ordinal logistic regression
NND	Categorical, ordinal, interval-scaled	Multinomial logistic regression
Categorical		
	Categorical, ordinal	χ^2 or Fisher exact test
	Categorical, ordinal or interval	(Multinomial) logistic regression

ND, Normally distributed; NND, not normally distributed.

which analyses will be performed in advance of the study and document which analyses were agreed upon a priori versus post hoc.

PRIMARY VERSUS SECONDARY OUTCOMES

Similarly, it is important to determine the primary and/or secondary outcomes a priori. Generally, RCTs and interventional studies will have these decided upon at the time of study registration. However, there is often a reporting bias in favor of significant effects, and the distinction between primary and secondary outcomes is sometimes neglected. The astute reader should be alert to the distinction between primary and secondary outcomes. This is obviously an important issue with respect to efficacy of a novel intervention. Moreover, the primary outcome is generally the rationale for power and sample size calculations. The interpretation of nonsignificant findings for secondary outcomes may be limited by insufficient power.

HOW TO IDENTIFY APPROPRIATE USE OF STATISTICS

The misuse of statistical methods is common in the dermatology and medical literature. The discerning reader needs to be able to recognize the misuse of statistical tests and be able to interpret the results with a grain of salt. In order to do this, a fundamental understanding of some of the more common statistical tests is needed. The next section reviews some of the most commonly used statistical

tests and summarizes the key aspects for their appropriate use (Table I), including data type, distribution, sample size, and study design.

DO THE STATISTICS FIT THE DATA?

Key points

- Dependent variable is an outcome or response variable of the study
- Independent variable is an exposure or explanatory variable of the study
- There are 3 major data types: categorical, ordinal-scaled, and interval-scaled

There are 3 major data types: categorical, ordinal-scaled, and interval-scaled. Categorical data can be represented either by character strings or numbers and are limited to unordered classifications. An example of categorical data is race and/or ethnicity, which may include African American, white, Asian, Hispanic, et cetera. These categories represent distinct groups that are not ordered on any meaningful scale.

Ordinal-scaled data represent classifications where the classes have some kind of ordering to them. An example of ordinal-scaled data is severity of a disease, which may include ordered categories, such as mild, moderate, and severe disease. The categories represent distinct groups but are related by an order where moderate is more severe than mild, et cetera.

Finally, interval-scaled data can be either continuous or discrete (noncontinuous). Continuous variables have numeric values that can occur at any point within some interval. For example, age can be

treated as a continuous variable because a person's age could take on any value between 0 and >100 years. Discrete variables have numeric values that are limited to particular individual values. For example, in a theoretical study of the association of nevus counts and the risk of malignant melanoma, the number of nevi will be in whole numbers without any fractional sizes. The counts are not continuous, but are still numeric and ordered with a consistent interval-scale.

The first step to identify the appropriate use of statistical methodology is to recognize the data type for the predictor and outcome variables. The repertoire of statistical tests for continuous outcome variables includes *t* tests and analysis of variance (ANOVA), the nonparametric equivalents Kruskal-Wallis and Wilcoxon tests, Pearson and Spearman correlations, linear regression, and general linear models. The repertoire of statistical tests for categorical and ordinal outcome variables includes χ^2 and Fisher exact tests and binary, ordinal, and multinomial logistic regression (Table I).

PARAMETRIC VERSUS NONPARAMETRIC TESTS

Key points

- There are several ways of approaching nonnormally distributed data, including the use of nonparametric methods, data transformations, or conversion to an ordinal/categorical variable
- Readers and reviewers of the literature should be cautious about the interpretation of results from studies with small sample sizes using parametric testing

The next step to identify the appropriate use of statistical methodology is to determine the distribution of the data. An assumption behind most parametric tests of means (eg, *t* test and ANOVA) is that the data be normally distributed (ie, symmetric and bell-shaped). There are 2 common ways of approaching nonnormally distributed continuous data: the use of nonparametric methods (eg, Kruskal-Wallis and Wilcoxon tests) or using a transformation of the outcome variable (eg, log or square root). Readers and reviewers of the literature should be cautious about the interpretation of results from studies with small sample sizes or highly skewed data using parametric testing, such as *t* tests or ANOVA. The definition of small, intermediate, or large sample sizes is somewhat arbitrary, ranging from $n = 15$ to $n = 30$ or even $n = 100$. Studies with larger sample sizes (>100 per group) may be

amenable to parametric tests even when the outcome variable is not normally distributed by applying the central limit theorem. The central limit theorem tells us that as the sample size increases, the mean of the sampling distribution approaches normality. However, the central limit theorem and parametric testing should not be applied when variables have extremely skewed distributions or heteroscedasticity.

A third approach to a nonnormally distributed outcome variable is to convert it to a categorical or ordinal variable. Commonly used summary statistics, including mean and median, are typically inappropriate for multimodal data (multiple peaks in the distribution). An example of this is found in a study that found bimodal serum vitamin D levels in vitiligo patients.¹² In that scenario, consideration of vitamin D as a continuous variable with normal distribution was inappropriate because the distribution was bimodal. Rather, vitamin D levels were divided into 2 groups—high and low—using a predetermined cut-point.

DO THE STATISTICS FIT THE STUDY DESIGN?

Specific consideration of the study design is necessary when selecting an appropriate statistical model. For example, longitudinal studies are vulnerable to attrition bias and should use person-time methods, such as Kaplan-Meier plots or Cox proportional hazards regression. Matched studies must factor the matching variable into statistical models. Ideally, models should be stratified by the matching variable, such as conditional logistic regression. Multicenter studies may be biased by differences at some sites and models may need to adjust for random effects from different sites, such as mixed models. The astute reader should be alert to these considerations because they can change the results of a study. For example, I recently performed a matched case-control study that found that obesity is a risk factor for development of AD. The study used conditional logistic regression and found an odds ratio of 2.15 for obesity compared with normal weight.¹³ In contrast, the results were no longer significant in unconditional models that did not account for the matching variable (unpublished data).

The above stepwise approach is outlined in Table I: first, identify the outcome variable type (interval-scaled, ordinal, or categorical), and if the outcome is interval-scaled, identify whether it is normally or not normally distributed; second, identify the predictor variable type (interval-scaled,

ordinal, or categorical), and if the predictor is categorical, identify the number of groups (≥ 2).

Additional considerations include the cell frequencies for categorical variables (<5, Fisher exact test; ≥ 5 : χ^2 test), matching (conditional logistic regression), study designs (longitudinal, Cox proportional hazards regression; case-control, logistic regression), and number of centers (multicenter, mixed models with random effects for study site).

STANDARD DEVIATION VERSUS STANDARD ERROR OF THE MEAN

Key points

- Standard deviation is a measure of variability of a data distribution
- It is incorrect to use standard error of the mean as a measure of spread or variability of a data distribution

Standard deviation is a measure of variability of a data distribution (ie, by how much, on average, each observation varies from the sample mean). In contrast, standard error of the mean (SEM) is a measure of how well the sample mean of the observed study group approximates the actual mean of some underlying population. It is calculated by dividing the standard deviation by the square root of N; the larger the sample, the better the sample mean of the observed study group approximates the whole population mean. The SEM is therefore smaller than the standard deviation because it is divided by a denominator > 1 . It is incorrect to use SEM as a measure of spread or variability of a data distribution.

Unfortunately, SEM is commonly misused in the medical literature. Two recent critical reviews of 4 obstetrics and gynecology and 4 anesthesia journals found that 13.6% (range, 2.9-22.68%)¹⁴ and 23% (range, 11.5-27.7%)¹⁵ of articles, respectively, inappropriately reported SEM. The discerning reader and reviewer should be alert for this practice because it may dramatically underestimate the actual variability between observations. Because there are multiple approaches to presenting variability (eg, mean vs median and standard deviation and interquartile range), it is also imperative for measurements of variability to be clearly labeled in graphs and tables.

EXAMPLES OF HOW IMPROVED STUDY DESIGN RESOLVED CONTROVERSIES IN DERMATOLOGY

Key points

- Well-designed, large-scale prospective studies may have contradictory results with and offer

a higher level of scientific evidence than retrospective studies

- Metaanalyses summarize the results of multiple studies and can be used to compare treatments, even when head-to-head studies are lacking
- Observational studies are needed when randomized controlled trials are not feasible, such as studies of a known harmful exposure that is unethical to assign patients

The following 5 scenarios illustrate the impact of proper study design on answering common clinical questions.

Question 1. Does sunscreen usage prevent melanoma? Dermatologists are constantly providing recommendations on sunscreen usage to patients. Previous well-designed RCTs found that regular sunscreen use can prevent cutaneous squamous cell cancer.^{16,17} However, multiple case-control studies that were subject to retrospective recall bias were inconclusive; some found that sunscreen increased the risk of melanoma, while others found a protective effect.^{18,19} The ideal study design to answer this question is a long-term, prospective, RCT that compares melanoma incidence in subjects with diligent application of sunscreen with a well-matched control group that applies vehicle alone. Indeed, an Australian study using such a design found that sunscreen protects against melanoma, particularly invasive melanoma.²⁰

Question 2. Does sentinel lymph node biopsy and lymph node dissection improve mortality in malignant melanoma? Several large, retrospective case series, cohort studies, and small uncontrolled prospective studies were inconsistent; some found improved survival after lymph node dissection; others did not.²¹⁻²⁴ The ideal study design to answer this question is a prospective RCT comparing long-term mortality rates of melanoma patients treated with wide excision and sentinel lymph node biopsy and lymph node dissection with a well-matched group undergoing wide excision alone. The first such study was an international multicenter RCT, which found no survival benefit for regional lymph node dissection in patients without any nodal or distant metastases.²⁵ More recently, the even larger Multicenter Selective Lymphadenectomy Trial allowed for comparison of the impact of biopsy and dissection between nodal-positive and -negative patients. They also found that sentinel lymph node mapping and biopsy did not improve 5-year melanoma-specific survival overall. However, immediate lymphadenectomy significantly improved 5-year survival rates in

patients with nodal metastases.²⁶ While there are still many questions left unanswered, these well-designed studies have helped answer an important clinical question.

Question 3. Does obesity cause AD? Multiple questionnaire-based case-control studies that were subject to retrospective recall bias found inconsistent results; some found that obesity increased risk, decreased risk, or had no risk difference for AD.²⁷⁻³⁰ The ideal study design to answer this question is a prospective, randomized, longitudinal observational study that compares the incidence of AD in obese and well-matched healthy weight subjects who were not yet diagnosed with AD. Silverberg et al¹³ performed a retrospective clinical longitudinal study and found that prolonged obesity early in life is associated with increased risk of AD.¹³ Murray et al³¹ performed a prospective birth cohort study and found that increasing body mass index was significantly associated with an increased odds of eczema at 5 and 8 years of age.³¹ These longitudinal studies that controlled for age and other confounding factors show that obesity preceded the onset of and confers increased risk for AD.

Question 4. Which acne treatment is better in women: oral antibiotics or oral combined estrogen-progesterone contraceptive pills (OCPs)? Multiple previous studies found efficacy of both as acne treatments, though only 1 study performed a head-to-head comparison of tetracycline and estrogen-cyproterone acetate in a RCT and found comparable efficacy after 6 months of treatment.³² To fill the gap left by the dearth of head-to-head comparisons, a recent metaanalysis pooled the results of 19 studies of oral antibiotics and 13 studies of OCPs and compared their effects on reducing clinical lesions.³³ They found that oral antibiotics were superior after 3 months of treatment, but there were no differences observed after 6 months of treatment. This study provides important high-level evidence in support of OCP monotherapy for acne in women.

Question 5. Does cigarette smoking cause nonmelanoma skin cancer (NMSC)? The “ideal” study design would be a large-scale RCT with randomization of persons to either cigarette smoking or no smoking and following them for several decades to determine if they developed skin cancer. However, such a study is neither feasible nor ethical because of the known myriad other harmful effects of smoking. We are forced to rely on observational studies of persons for whom smoking status is already established. However, observational studies may be conducted using multiple designs, be of poor quality, and often have conflicting results. A recent

metaanalysis of 23 observational studies examining the association between smoking and skin cancer found that smoking was associated with higher odds of squamous cell carcinoma but not basal cell carcinoma.³⁴ Of note, many of the included studies were of moderate quality. Nevertheless, metaanalysis of these observational studies provides the best evidence to date on the role of smoking in NMSC.

CONCLUSIONS

Critical evaluation of the clinical and epidemiologic dermatology literature can be daunting. The present review provides a foundation for such critical evaluation and identification of major pitfalls in various study designs. In addition, clinicians are able to determine the clinical relevance of a study by paying attention to the level of evidence offered therein. A review of these principles will augment the clinical dermatologist’s ability to critically assess the dermatology literature and incorporate cutting edge research studies into clinical practice with an evidence-based approach.

REFERENCES

1. Strasak AM, Zaman Q, Pfeiffer KP, Göbel G, Ulmer H. Statistical errors in medical research—a review of common pitfalls. *Swiss Med Wkly*. 2007;137:44-49.
2. Wu S, Jin Z, Wei X, et al. Misuse of statistical methods in 10 leading Chinese medical journals in 1998 and 2008. *ScientificWorldJournal*. 2011;11:2106-2114.
3. Neville JA, Lang W, Fleischer AB Jr. Errors in the *Archives of Dermatology* and the *Journal of the American Academy of Dermatology* from January through December 2003. *Arch Dermatol*. 2006;142:737-740.
4. Margolis DJ, Apter AJ, Gupta J, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. *J Allergy Clin Immunol*. 2012;130:912-917.
5. Ilakovac V. Statistical hypothesis testing and some pitfalls. *Biochem Med*. 2009;19:6-10.
6. Ayeni O, Dickson L, Ignacy TA, Thoma A. A systematic review of power and sample size reporting in randomized controlled trials within plastic surgery. *Plast Reconstr Surg*. 2012;130:78e-86e.
7. Abdul Latif L, Daud Amadera JE, Pimentel D, Pimentel T, Fregni F. Sample size calculation in physical medicine and rehabilitation: a systematic review of reporting, characteristics, and results in randomized controlled trials. *Arch Phys Med Rehabil*. 2011;92:306-315.
8. Silverberg JI, Norowitz KB, Kleiman E, et al. Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: a case-control study. *J Allergy Clin Immunol*. 2010;126:300-305.
9. Benjamini Y, Hochberg Y. Controlling the false discovery rate - a practical and powerful approach to multiple testing. *J Roy Stat Soc B Met*. 1995;57:289-300.
10. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Stat*. 2001;29:1165-1188.
11. Walenkamp MM, Roes KC, Bhandari M, Goslings JC, Schep NW. Multiple testing in orthopedic literature: a common problem? *BMC Res Notes*. 2013;6:374.

12. Silverberg JI, Silverberg AI, Malka E, Silverberg NB. A pilot study assessing the role of 25 hydroxy vitamin D levels in patients with vitiligo vulgaris. *J Am Acad Dermatol.* 2010;62: 937-941.
13. Silverberg JI, Kleiman E, Lev-Tov H, et al. Association between obesity and atopic dermatitis in childhood: a case-control study. *J Allergy Clin Immunol.* 2011;127: 1180-1186.e1.
14. Ko WR, Hung WT, Chang HC, Lin LY. Inappropriate use of standard error of the mean when reporting variability of study samples: a critical evaluation of four selected journals of obstetrics and gynecology. *Taiwan J Obstet Gynecol.* 2014;53: 26-29.
15. Nagele P. Misuse of standard error of the mean (SEM) when reporting variability of a sample. A critical evaluation of four anaesthesia journals. *Br J Anaesth.* 2003;90:514-516.
16. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet.* 1999;354:723-729.
17. van der Pols JC, Williams GM, Pandeya N, Logan V, Green AC. Prolonged prevention of squamous cell carcinoma of the skin by regular sunscreen use. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2546-2548.
18. Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am J Public Health.* 2002;92: 1173-1177.
19. Dennis LK, Beane Freeman LE, VanBeek MJ. Sunscreen use and the risk for melanoma: a quantitative review. *Ann Intern Med.* 2003;139:966-978.
20. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. *J Clin Oncol.* 2011;29:257-263.
21. Conrad FG. Treatment of malignant melanoma: wide excision alone vs lymphadenectomy. *Arch Surg.* 1972;104:587-593.
22. Goldsmith HS, Shah JP, Kim DH. Prognostic significance of lymph node dissection in the treatment of malignant melanoma. *Cancer.* 1970;26:606-609.
23. Hansen MG, McCarten AB. Tumor thickness and lymphocytic infiltration in malignant melanoma of the head and neck. *Am J Surg.* 1974;128:557-561.
24. Breslow A. Tumor thickness, level of invasion and node dissection in stage I cutaneous melanoma. *Ann Surg.* 1975; 182:572-575.
25. Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *N Engl J Med.* 1977;297:627-630.
26. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med.* 2006; 355:1307-1317.
27. Mai XM, Nilsson L, Axelson O, et al. High body mass index, asthma and allergy in Swedish schoolchildren participating in the International Study of Asthma and Allergies in Childhood: phase II. *Acta Paediatr.* 2003;92:1144-1148.
28. Violante R, del Rio Navarro BE, Berber A, Ramirez Chanona N, Baeza Bacab M, Sierra Monge JJ. Obesity risk factors in the ISAAC (International Study of Asthma and Allergies in Childhood) in Mexico City. *Rev Alerg Mex.* 2005;52:141-145.
29. Vlaski E, Stavric K, Isjanovska R, Seckova L, Kimovska M. Overweight hypothesis in asthma and eczema in young adolescents. *Allergol Immunopathol (Madr).* 2006;34:199-205.
30. von Kries R, Hermann M, Grunert VP, von Mutius E. Is obesity a risk factor for childhood asthma? *Allergy.* 2001;56:318-322.
31. Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, Custovic A. Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Exp Allergy.* 2011;41:78-85.
32. Greenwood R, Brummitt L, Burke B, Cunliffe WJ. Acne: double blind clinical and laboratory trial of tetracycline, oestrogen-cyproterone acetate, and combined treatment. *Br Med J.* 1985;291:1231-1235.
33. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. *J Am Acad Dermatol.* 2014;71:450-459.
34. Leonardi-Bee J, Ellison T, Bath-Hextall F. Smoking and the risk of nonmelanoma skin cancer: systematic review and meta-analysis. *Arch Dermatol.* 2012;148:939-946.

Human papillomavirus vaccine trials and tribulations

Clinical perspectives

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Learning objectives

After completing this learning activity, participants should be able to state the recommended human papilloma virus immunization schedule for females and males; list the oncogenic and nononcogenic human papilloma virus types for which each of the three human papilloma virus vaccines provide immunity; and discuss the evidence that the human papilloma virus vaccination does not encourage unsafe sexual behavior in children and adolescents.

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Human papillomavirus (HPV) affects hundreds of millions of people worldwide and is associated with both benign and malignant neoplasms in men and women. It is a double-stranded DNA virus with an icosahedral capsid. Forty HPV types are known to infect mucosal keratinocytes. If not cured by the immune system, the infection can lead to genital warts, mucosal dysplasia, or cancer. The most common oncogenic types are 16 and 18. The vaccine to prevent HPV and its associated morbidity and mortality has existed since 2006. Several variations protect against an increasing number of HPV types. The recommended vaccination age is before sexual exposure; administration of the vaccine to children has been controversial. This continuing medical education review evaluates the current HPV vaccines available to clinicians. Part I focuses on the debate over who should be vaccinated, at what age, and in which populations. (J Am Acad Dermatol 2015;73:743-56.)

Key words: anal cancer; Cervarix; cervical cancer; condylomas; Gardasil; human papillomavirus; vaccine.

INTRODUCTION

Key points

- Not all human papillomaviruses are oncogenic
- Existing vaccines target human papillomavirus types that cause benign and oncogenic neoplasms

- Most human papillomavirus infections are suppressed by the body's immune system

Human papillomavirus (HPV) is transmitted by skin-to-skin or mucosa-to-mucosa contact. There are >150 HPV types, with approximately 60% causing benign neoplasms (warts) on locations

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Abbreviations used:

AIN:	anal intraepithelial neoplasia
CDC:	Centers for Disease Control and Prevention
CHMP:	European Committee for Medicinal Products for Human Use
FDA:	US Food and Drug Administration
HPV:	human papillomavirus
MSM:	men who have sex with men
MSW:	men who have sex with women
OPSCC:	oropharyngeal squamous cell carcinoma
USPSTF:	US Preventive Services Task Force
VLP:	virus-like particle
SCCA:	squamous cell carcinoma of the anus

such as the hands and feet, and 40% that infect mucosal surfaces, including the genitals, anus, and oropharynx, usually by sexual activity.¹ Most HPV infections are asymptomatic; those affected are typically not aware that they have the virus. Each year, 14 to 20 million people in the United States are infected with the virus; 79 to 110 million Americans are currently infected.²⁻⁴ While most HPV infections are resolved by the body's immune system and never result in human health problems, some people develop benign genital warts, while others, affected by specific oncogenic types of HPV, develop cancer of the cervix, oropharynx, anus, vulva, vagina, and penis.² In 2006, the US Food and Drug Administration (FDA) and the European Committee for Medicinal Products for Human Use (CHMP) approved the first HPV vaccine—a quadrivalent HPV vaccine—marketed as Gardasil (Merck and Co, Kenilworth, NJ). Gardasil targets oncogenic HPV types 16 and 18, as well as types 6 and 11, which produce genital warts. HPV type 16 causes about 50% of cervical cancers; HPV type 18 causes an additional 20% of cervical cancers.⁵ In certain circumstances, HPV types 6 and 11 are responsible for condylomas that have the potential to become squamous cell carcinomas, such as Buschke–Lowenstein tumor,⁶ oral florid papillomatosis,⁷ and epithelioma cuniculatum.⁸ Approved by Australia in May 2007, the CHMP in September 2007, and the FDA in October 2009, a bivalent HPV vaccine, marketed as Cervarix (GlaxoSmithKline, New York, NY), is designed to prevent infection from oncogenic HPV types 16 and 18 only.^{1,9} On December 10, 2014, the FDA approved a 9-valent HPV vaccine for the prevention of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, which has been marketed as Gardasil-9 (Merck and Co; Fig 1).¹¹

CERVICAL HUMAN PAPILLOMAVIRUS**SCREENING****Key points**

- **In the United States, it is recommended that women receive screening examinations for cervical dysplasia**
- **The Papanicolaou smear detects dysplasia of epithelial cells, not direct human papillomavirus infection**
- **Examination intervals may be extended from 3 to 5 years if a human papillomavirus test is added to the Papanicolaou smear**

The US Preventive Services Task Force (USPSTF) recommends that women between 21 and 65 years of age with a cervix be screened with a Papanicolaou (Pap) smear every 3 years, or every 5 years between 30 and 65 years of age, with a combination of a Pap smear and HPV testing, for cervical cancers and precancers.¹² Pap smears are performed at the recommended intervals in the majority of developed countries;¹³ low- and middle-income countries (eg, India, China, South Africa, Nigeria, and Indonesia) do not have organized cervical cancer screening programs. Although it is unclear how representative California is with respect to Pap smears in the United States, a 2005 survey in California asked women if they had received a Pap smear in the previous 3 years. The results revealed that cervical cancer screening rates were similar among black, Hispanic, and non-Hispanic white women, with rates ranging from 74% to 80%. Asian American women had lower rates (60%) of screening in the previous 3 years.¹⁴ Although screening rates are similar among the populations, treatment delay does exist for black women as compared to white or Hispanic women.¹⁴⁻¹⁷

HUMAN PAPILLOMAVIRUS**EPIDEMIOLOGY****Key points**

- **Human papillomavirus infection rates vary by country**
- **Infection by human papillomavirus is the most common sexually transmitted infection**
- **More than 600,000 cancers are attributed to human papillomavirus infection worldwide**

The worldwide HPV infection rate among women of all ages is 12%, with a peak of 24% among those who are tested after they become sexually active and who are also under 25 years of age.¹⁸ The prevalence is highest among women in sub-Saharan Africa (24%), Central and Eastern Europe (21%), and the Caribbean (35.4%).¹⁸ HPV infection is the most

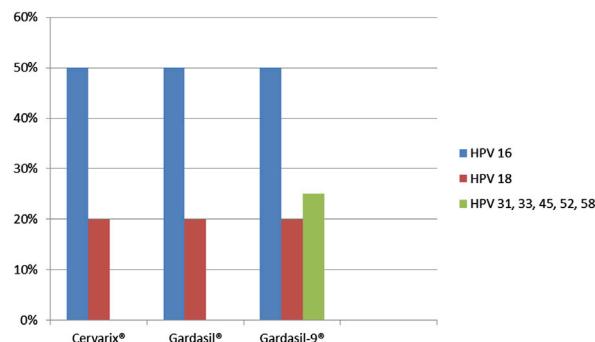


Fig 1. Oncogenic human papillomavirus types as covered by the existing vaccine and their frequency in worldwide cervical cancer.¹⁰

common sexually transmitted disease, although it is usually cured by the immune system. Worldwide, the risk of being infected at least once among both men and women is 50%.¹⁹ Mortality from HPV is caused by oncogenic HPV types whose infections lead to dysplasia and cervical cancer. Patients 20 to 24 years of age have the highest prevalence of either oncogenic or nononcogenic infection²⁰ (Fig 2). The Centers for Disease Control and Prevention (CDC) estimates the incidence of new HPV-associated cancers in the United States at 26,800 per year^{21,22} (Fig 3; Table I). In Europe, HPV types 16 and 18 are linked to almost 50,000 new cancers per year. Of the 610,000 cancers attributed to HPV worldwide per year among both men and women, 527,624 were cervical cancer, resulting in 265,653 deaths.¹⁸ The majority (230,158 cases) occurred in less developed regions.²³ HPV infection causes 99.7% of cases of cervical cancer.²⁴ Globally, cervical cancer is the third most commonly diagnosed cancer and the fourth most frequent cause of death from cancer in women.²⁵

HPV also is found in oropharyngeal squamous cell cancer (OPSCC). Each year in the United States, there are 9000 HPV-related oropharyngeal cancers, and between 90% and 95% of these patients are infected with HPV 16.^{21,22,26} In the United States and Sweden, there has been a rise in percent of patients with OPSCC that test positive for oncogenic HPV.²⁷ Between the 1980s and 2000s, that percentage has risen from 16.3% to between 18% and 72.7%.²⁸⁻³¹ The reason for the increase in HPV-related OPSCCs is unknown. HPV is believed to be the causative agent in many types of OPSCC³²: by either decreasing the immune response to dysplastic keratin or accelerating carcinogenesis.³³ The rate of oropharyngeal cancer is 6.2 per 100,000 in men and 1.4 per 100,000 in women. In Slovenia, 20.2% of patients diagnosed with OPSCC had HPV-positive tumors.³⁴

As with cervical exposure, the majority of people who have anal epithelial infection with HPV will experience resolution of the infection. Those who are exposed to an oncogenic type and unable to clear it may develop anal epithelial cell dysplasia or cancer. In the United States and Europe, the incidence rate of squamous cell carcinoma of the anus (SCCA), which typically presents at 60 years of age, is 1 in 100,000 among men and women, while cervical cancer is between 6.5 and 7.8 cases per 100,000 people. There is some worldwide variation; the prevalence of HPV-associated anal cancer in Europe, the United States, and Canada is approximately 84%, while in Thailand and Japan it is associated 96% of the time.^{35,36} Anal cancers are primarily linked to infection from HPV type 16.³⁶ Anal sex provides a high risk of HPV exposure, with exposure to oncogenic or nononcogenic types at rates between 70% and 90%.³⁷ The prevalence of HPV of any type among men who have sex with men (MSM) is 26%; among MSM with HIV, the rate is 86%.^{38,39} The prevalence of HPV type 16 ranges from 28% to 35% in MSM with HIV and 12.5% in MSM without HIV.^{39,40} In the United States, the rate of SCCA is 1.8 per 100,000 in women and 1.2 per 100,000 in men.^{5,22,41}

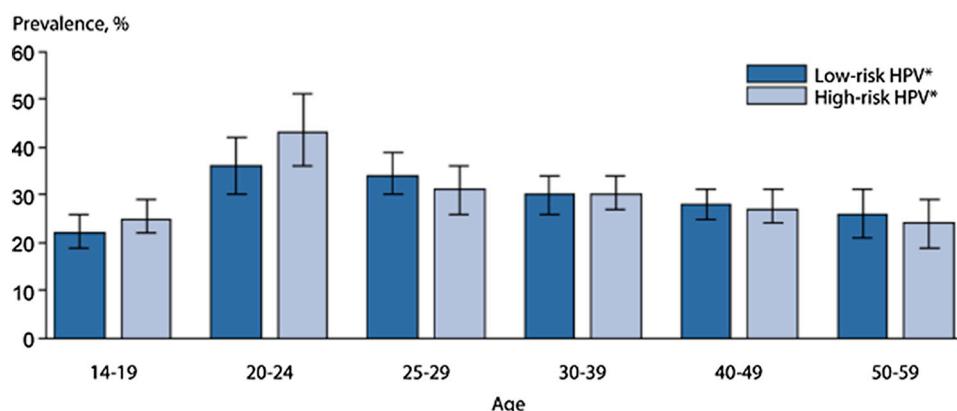
The incidence of anogenital warts (AGWs) in Europe, Canada, and the United States, 90% of which are caused by HPV types 6 and 11⁴²—ranges from 99.95 to 170.8 per 100,000 people.⁴³⁻⁴⁶ The rate is higher in larger cities. AGWs are initially diagnosed by gynecologists in women 71.7% of the time and dermatologists 7.9% of the time, while in men AGWs are most commonly diagnosed by dermatologists (44.8%).⁴³

There are approximately 11,000 penile cancers worldwide per year associated with HPV type 16 and 8000 penile cancers associated with HPV type 18.⁴⁷ In European and North American countries, the incidence ranges from 0.3 to 1.0 per 100,000 men.⁴⁸ Ninety-five percent of penile cancers are squamous cell carcinomas; HPV DNA is found 50% to 63% of the time.^{47,49} HPV 16 is the most common type found in patients with penile cancer, followed by HPV types 18, 6, and 11.^{31,50} Most patients infected do not develop cancer but may develop anogenital warts. As in HPV-driven cervical cancer, DNA methylation is essential for development of HPV-induced penile cancer.⁵¹

RISK FACTORS FOR HUMAN PAPILLOMAVIRUS ACQUISITION

Key points

- There is a higher mortality rate from cervical cancer in developing countries compared to developed countries



* HPV = human papillomavirus.

NOTE: Error bars indicate 95% confidence interval. Both high-risk and low-risk HPV types were detected in some females.

Fig 2. Human papillomavirus prevalence of oncogenic and nononcogenic types among women 14 to 59 years of age in the United States. Courtesy of the Centers for Disease Control and Prevention (<http://www.cdc.gov/std/stats12/figures/45.htm>).

- **Tobacco use, sharing of toothbrushes or lipstick, the number of sexual partners, and a history of oral–genital and coital sexual acts is associated with increased human papillomavirus infection rates**
- **Squamous cell carcinoma of the anus is associated with tobacco use and infection with oncogenic human papillomaviruses**

In the United States, women at highest risk for infection of both oncogenic and nononcogenic HPV types are low-income, black women compared to white and Mexican American women.⁵² Although the authors do not speculate why—and did not evaluate all Hispanic subgroups—among the latter groups, married Mexican American women are less likely than married white women to be infected with HPV.⁵² Worldwide, there is increased mortality from cervical cancer among women in developing nations compared to those living in developed countries. Oral HPV infections are on the rise. The risk of contracting oral HPV is higher among men who have a female partner with an oral or genital HPV infection compared to men with female partners who do not have an HPV infection.⁵³ There is also increased prevalence of oral HPV infection among men who have smoked cigarettes or had a higher number of lifetime sexual partners.⁵³ Among women, oral HPV risk factors include women who smoke cigarettes, share toothbrushes or lipstick, have a greater number of lifetime sexual partners or who engaged in deep kissing, or those who have participated in oral–genital and coital sexual acts.⁵⁴ In the course of vaginal intercourse, there is a greater risk of transmission of HPV from female-to-male than contraction by a woman from an infected man.⁵⁵ An Italian

study found that HIV-infected MSM have a higher risk of HPV prevalence (93.3%) compared to similar aged MSM who do not have HIV (72.4%).⁵⁶ Risk factors for SCCA include infection from oncogenic HPV, smoking,^{57,58} receptive anal intercourse, lack of condom use, nutritional deficiencies, older age, and immunosuppression, such as HIV or post–organ transplant medications.⁵⁸

HUMAN PAPILLOMAVIRUS

Key points

- **The human papillomavirus is a double-stranded DNA papillomavirus**
- **The infection is believed to infect keratinocytes and remain dormant, suppressed by the immune system**
- **The majority of genital warts develop 2 to 3 months after infection**

A virus with double-stranded circular DNA from the papillomavirus family, HPV infects skin and mucous membrane keratinocytes. Although only 40 HPV types are known to invade mucosal surfaces, there are >150 HPV types that have been identified. If not resolved by the body's immune system, some HPV types produce genital warts, which may become evident as soon as 3 weeks, with a majority developing after 2 to 3 months of infection.⁵⁹ Other HPV types may lead to squamous intraepithelial dysplasia and cancer.^{24,59} Warts may develop later in life because the virus may remain dormant until the immune system is suppressed.⁶⁰ All HPVs have icosahedral capsids.⁶¹ The HPV genome contains 8 genes and splice variants that encode genes transcribed early in viral replication; these are referred to

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)			Percentage probably caused by HPV	Number probably caused by HPV [†]		
	Male	Female	Both Sexes		Male	Female	Both Sexes
Anus	1,549	2,821	4,370	91%	1,400	2,600	4,000
Cervix	0	11,422	11,422	91%	0	10,400	10,400
Oropharynx	9,974	2,443	12,417	72%	7,200	1,800	9,000
Penis	1,048	0	1,048	63%	700	0	700
Vagina	0	735	735	75%	0	600	600
Vulva	0	3,168	3,168	69%	0	2,200	2,200
TOTAL	12,571	20,589	33,160		9,300	17,600	26,900

[†]Individual cells may not sum to total due to rounding.

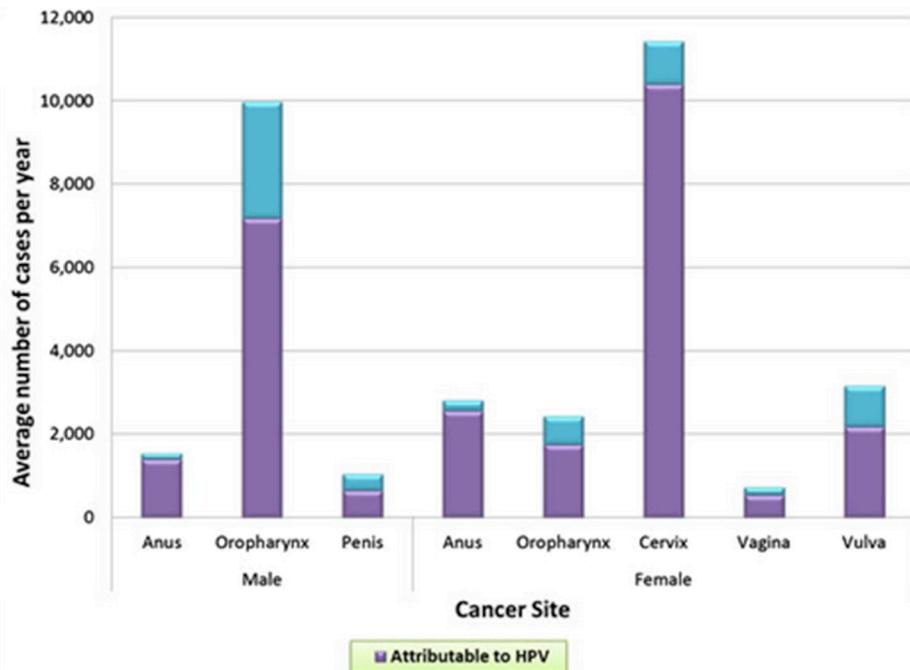


Fig 3. Human papillomavirus–attributed cancers among human papillomavirus–associated cancer sites in the United States. Courtesy of the Centers for Disease Control and Prevention (<http://www.cdc.gov/cancer/hpv/statistics/cases.htm>).

Table I. Number of cancer cases attributed to human papillomavirus infection per year in the United States*

Cancer site	No. of cases caused by human papillomavirus infection [†]		
	Male	Female	Both sexes
Anus	1400	2600	4000
Cervix	0	10,400	10,400
Oropharynx	7200	1800	9000
Penis	700	0	700
Vagina	0	600	600
Vulva	0	2200	2200
Total	9300	17,600	26,900

*Adapted from the Centers for Disease Control and Prevention.²¹

[†]Individual cells may not sum to total because of rounding.

as E genes (Fig 4). They include genes that express nonstructural proteins needed for DNA replication, transcription, or viral assembly and release. Genes transcribed late, abbreviated as L-genes, include L1 and L2, which encode viral capsid proteins referred to as L1 and L2, respectively.⁶³ The papillomavirus capsid is made of 2 structural proteins: the major basic protein (L1) and the minor basic protein (L2).⁶⁴ Each capsid contains 72 pentameric capsomeres, each made of 5 L1 and L2 proteins.⁶⁴ Viral assembly occurs in the nucleus of the cell; L1 protein self-assembles into virus-like particles, while L2 has a lesser known role, but may be involved with virion production.⁶⁵ HPV is believed to enter the body via cutaneous or mucosal trauma. After the immune

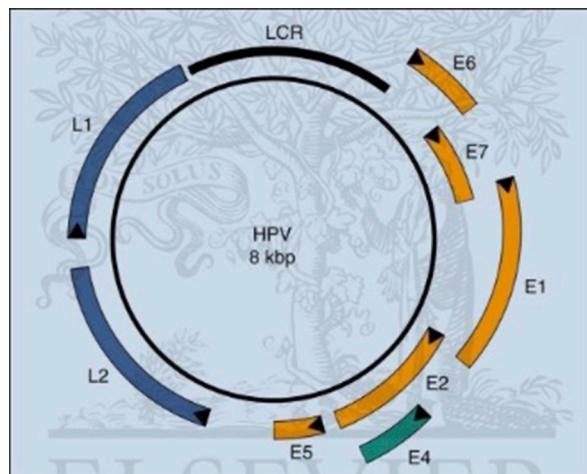


Fig 4. Map of the human papillomavirus genome. The circle indicates the approximately 7900-bp circular double-stranded DNA genome of HPV16 as found in viral particles and infected cells. The boxes outside the circle are the various translational open reading frames (ORFs) that encode the viral proteins. They include the early (E) and late (L) ORFs.⁶² (Used with permission of Elsevier.)

system resolves the infection, the virus may remain dormant within the squamous cell⁶⁶ that will not be dysplastic; Papanicolaou (Pap) smears may be normal. The dormant virus will also be nontransmissible until a patient is immunosuppressed, at which time it may cause differentiation of the basal epithelial cells of the infected host.^{60,67} When integrated into the host squamous epithelial cell genome, the high-risk HPV types (16 and 18) will express gene E6, which will degrade tumor suppressor protein p53.⁶⁸ E7, also expressed early, is an oncoprotein that binds the tumor suppressor retinoblastoma protein (pRB) and allows HPV DNA synthesis.⁶⁹⁻⁷¹ E1 protein increases viral genome replication, E2 decreases the expression of E6 and E7.⁵⁸ Loss of E2 repression function leads to dysregulation of viral E6 and E7 oncogenes.⁷² The level of soluble TNF-alfa receptors may have an inverse correlation to the growth of HPV tumors.⁷³

VACCINE

Key points

- Each human papillomavirus vaccine uses inactive L1 proteins specific for a specific human papillomavirus type
- Antibodies are made for the specific L1 protein present in the vaccine
- In order to increase the immune system's reaction to the vaccine, an adjuvant is added
- Human papillomavirus vaccines do not eradicate existing infections

Table II. Human papillomavirus vaccines and human papillomavirus types given protection

	Gardasil*	Cervarix†	Gardasil-9*
HPV types	6, 11, 16, 18 and 18	6, 11, 16, 18, 31, and 18	33, 45, 52, and 58
Concentrations per dose, µg	20/40/40/20	20/20	30/40/60/40/20/20/20/20/20
Technology used to produce L1 VLPs	Yeast	Insect cell substrate	Yeast
Adjuvant used	AAHS	AS04	AAHS

AAHS, Amorphous aluminum hydroxyphosphate sulfate; AS04, aluminum hydroxide and 3-deacetylated monophosphoryl lipid A; L1, L gene 1; VLP, vaccine-like particle.

*Gardasil and Gardasil 9 are trademarks of Merck and Co (Kenilworth, NJ).

†Cervarix is a trademark of GlaxoSmithKline (New York, NY).

HPV vaccines are made of virus-like particles (VLPs) that contain inactive L1 HPV proteins—proteins from and specific to each type of HPV virus⁷⁴ (Table II). An adjuvant is used to stimulate an immune reaction to the vaccine antigen. In the quadrivalent vaccine, amorphous aluminum hydroxyphosphate sulfate is used as an adjuvant. In the bivalent vaccine AS04, 3-O-desacyl-4'-monophosphoryl lipid A absorbed onto aluminum is used.⁷⁵ Vaccination induces a strong immune response, more vigorous than to the natural infection, believed to result from an immune reaction to the VLPs and the L1 proteins.⁷⁴ The immune system subsequently creates antibodies to the specific L1 proteins present in the vaccine. These antibodies are expressed on the mucous membranes, neutralizing the presenting HPV virus immediately.⁷⁴ The quadrivalent vaccine Gardasil (Merck and Co) was approved by the FDA in 2006 for protection against HPV types 6 and 11, which cause genital warts—and rarely, nongenital warts⁷⁶—and oncogenic types 16 and 18.⁷⁷ The quadrivalent vaccine will not protect against anogenital disease other than HPV types 6, 11, 16, and 18.⁷⁸ Immune responses to the vaccine are equally efficacious between men and women.⁷⁹ In 2010, the FDA approved the quadrivalent vaccine for the prevention of anal cancer.⁸⁰ The efficacy of prevention of anal intraepithelial neoplasia (AIN) in MSM is 77.5%.⁸¹ The quadrivalent vaccine has been successful in preventing external genital warts in 90.4% of males 16 to 26 years of age.⁸² The CDC recommends that the 3-shot series should occur with the second shot 1 to 2 months after the first and the third shot 6 months after the first dose. The CDC also suggests that it is not necessary to restart the 3-shot vaccination series even if only 1 or 2 doses were ever

given or if months or years have passed before receiving the subsequent dose.² In 2009, a bivalent vaccine (Cervarix; GlaxoSmithKline) was approved for the prevention of HPV infections from types 16 and 18. On December 10, 2014, the FDA approved a 9-valent HPV vaccine (Gardasil-9; Merck and Co) that was approved to be given in 3 intramuscular doses to males 9 to 15 years of age and females 9 to 26 years of age.⁸³ As in the quadrivalent Gardasil vaccine, amorphous aluminum hydroxyphosphate sulfate is used as an adjuvant. The 9-valent HPV vaccine targets HPV type 16⁸⁴ (responsible for 50% of moderate and severe cervical intraepithelial neoplasia [CIN]), HPV type 18 (detected in 20% of cervical cancers⁸⁵) and types 31, 33, 45, 52, and 58, which are responsible for 25% of moderate and severe CINs, which may also lead to cancer.⁸⁶ Immunization against HPV types 6 and 11, which cause genital warts, are also included in the 9-valent vaccine.⁸⁶ Approval of the 9-valent vaccine was based on a randomized controlled study with 14,000 females 16 to 26 years of age; it noted efficacy of 97%, equal to that of the quadrivalent vaccine for HPV types 6, 11, 16, and 18.⁸⁷ No vaccine has proven to be therapeutic for patients who have existing HPV-induced lesions.⁸⁸

In the United States, all 3 licensed HPV vaccines are recommended to be given in 3 intramuscular doses, all of which should be administered before the individual becomes sexually active. Most countries have 3-dose HPV vaccination schedules, with doses given at 0-, 2-, and 6-month intervals. However, some governments are reducing immunization cost by only providing 2 doses over a 6- to 24-month period.⁸⁹ Currently, the length of immunity from 2 doses is unknown, but cohorts are being followed.⁹⁰ In 2013, Quebec changed their dosing from a 3-dose schedule to a quadrivalent 2-dose schedule for fourth-grade girls who were receiving immunization.^{90,91} In Switzerland and the United Kingdom, there are plans to provide the quadrivalent vaccine in 2 doses instead of 3 doses.⁹²

VACCINATION AND SEXUAL ACTIVITY

Key point

- Studies have not shown increased sexual activity among girls who have been vaccinated against human papillomavirus

Since the inception of the HPV virus, there have been parental concerns that providing a vaccine to prevent a sexually transmitted infection may encourage children and adolescents to engage in sexual activity.⁹³ A cohort of 1398 11- and 12-year-old girls was followed over a period of 3 years; 1

group was vaccinated against HPV and the other was not. The results showed virtually no difference between the 2 groups over that time period, with 2 girls in each group becoming pregnant and 1 vaccinated and 3 nonvaccinated girls receiving diagnoses of infection with chlamydia.⁹⁴ In 2013, the CDC released its most recent data of adolescent sexual behavior. Comparison of rates of sexual intercourse and condom use among 12th graders between 2005 (the year before the release of the HPV vaccine) and 2013 revealed virtually no change in either risk category.^{95,96} Changes in sexual behavior have been evaluated among females receiving the HPV vaccine. A questionnaire of 1243 females between 15 and 24 years of age revealed no association between those who had received the vaccine and an increased likelihood to be sexually active or an increased number of sexual partners.⁹⁷ Another study provided a questionnaire to girls 13 to 21 years of age who were sexually inexperienced before receiving the HPV vaccine and then a 6-month follow-up survey. The investigators found no change in sexual behaviors or link to vaccination and perception of sexual infection risk.⁹⁸ The same study evaluated 16- to 21-year-old females who were sexually experienced and found no change in their sexual behaviors after immunization.⁹⁸ A single study found a possible link between HPV vaccination and increased sexual activity. A survey conducted of girls 14 to 18 years of age did note a higher percentage (28.6%) of girls who at the time of survey had both had sexual intercourse and received the vaccine as compared to those who had not received the vaccine (17.8%). The interpretation is limited because the study did not determine whether sexual activity preceded HPV vaccination.⁹⁹

OPTIMAL VACCINATION AGE

Key points

- To be effective, the human papillomavirus vaccine must be received before infection
- The vaccine is recommended for girls as young as 11 years of age
- The quadrivalent vaccine is recommended for both boys and girls up to 26 years of age

To reduce persistent infection of HPV, which, if an oncogenic type, may lead to mucosal cancers, recipients of the vaccine must be immunized before infection. Because the virus is ubiquitous, immunization should occur before patients become sexually active. Some children are engaging in sexual intercourse before 12 years of age, and because of this the CDC Advisory Committee on Immunization Practices (ACIP) recommends that HPV vaccination be

initiated at 11 or 12 years of age. According to CDC data plotted on a Kaplan-Meier curve, 15% of African American males had engaged in sexual intercourse by 12 years of age, 42% by 14 years of age, and 82% by 17 years of age.¹⁰⁰ For Hispanic, Asian, and white males and females, as well as African American females, the rate of sexual activity by 12 years of age is <10% and—except for Hispanic males—<20% by 14 years of age. For Hispanic males, that rate is 23% by 14 years of age and 69% by 17 years of age. By age 17, the probability of sexual activity among Asian females is 28%, Asian males 33%, white females 58%, and 53% for white males. For Hispanic females, the rate of sexual activity before 17 years of age is 59%. For African American females, the rate of sexual activity by 17 years of age is 74%.¹⁰⁰ University students (ie, those 19–26 years of age) are currently a catch-up group because they were not vaccinated as children. This older age group may still benefit from HPV vaccination; a study found that 27% of American women at university (18–20 years of age) have not engaged in sexual intercourse and the other 73% averaged 1.8 sexual partners.¹⁰¹ This group can still benefit from vaccination because of their limited sexual exposure; 80.3% are not infected with any strain of HPV, and those who are have only 1 type.^{101,102} The current recommendation to vaccinate up to 26 years of age with the quadrivalent vaccine is a result of safety and efficacy studies that were used by the FDA to approve the vaccine. Recent studies have shown efficacy in vaccinating patients who are 24 to 45 years of age.¹⁰³ There are no safety or efficacy data regarding the vaccination of males >26 years of age.

VACCINATION OF BOYS AND GIRLS

Key points

- Human papillomavirus type 16 is responsible for the majority of anal cancers
- Human papillomavirus infections lead to penis, oropharyngeal, and anal cancer in men, as well as genital warts
- There is a 10% lifetime risk of genital wart development

Oncogenic HPV types have an affinity for infecting the immature squamous cells in both the anus and cervix. This area, referred to as the transformation zone, occurs where the outer cervix squamous epithelium transitions to columnar cells of the endocervix, and in the anus where the epithelium changes from the nonkeratinizing squamous epithelium of the anus to the columnar epithelium of the rectum.⁵ Vaccinating boys protects the transfer of

immunized HPV types to both male and female partners.¹⁰⁴ A study in 2008 of 2357 heterosexuals, both men and women, surveyed while at a clinic treating sexually transmitted diseases, revealed that 18.3% had engaged in anal sex in the previous 12 months.¹⁰⁵ In another study of men in São Paulo, Brazil, Cuernavaca, Mexico, and Tampa, Florida, the researchers found that 11.8% of men who had sex with women (MSW) engaged in anal sex with a woman in the preceding 6 months.¹⁰⁶ The study also noted the prevalence of oncogenic genital HPV of the anus or penis among MSW, MSM, and men who have sex with both women and men (MSWM) was 30.0%, 39.6%, and 29.7%, respectively.¹⁰⁶ The study results were limited because the frequency per group at each site was not stated. Virtually all anal cancers are a result of HPV infection, with HPV type 16 being the most frequent inducer. A metaanalysis of anogenital cancers in North America, Europe, Asia and South America revealed that HPV type 16 was found in >75% of HPV-positive non-cervical anogenital cancers.^{36,107} HPV vaccination of all females would decrease the incidence of female cancers and genital warts. However, immunization of females does not prevent men from developing HPV-induced cancers, such as cancers of the anus, oropharynx, penis, or genital warts.⁴¹

Nononcogenic HPV types result in genital warts in both men and women. In men from western, central, and Scandinavian Europe, the estimated number of new cases of genital warts attributed to HPV types 6 or 11 was estimated to be between 286,682 and 325,722 per year, with a lifetime risk of acquiring genital warts at 10%.⁴¹ Studies in the United States have found the lifetime risk to also be 10%.¹⁰⁸

MEN WHO HAVE SEX WITH MEN AND VACCINATION

Key points

- There is a higher rate of human papillomavirus infection among men who have sex with men as compared to men who have sex with women
- Anal Papanicolaou smears may be performed to detect dysplasia

Most anal infections caused by HPV in MSM are resolved by the immune system; this is also the case with women who engage in anal sex.³⁷ In 2011, a study in Amsterdam found that among HIV-negative MSM, there was a 70% anal infection rate with 1 of 7 oncogenic HPV types (ie, 16, 18, 31, 33, 45, 52, and 58). Testing of the skin of the penis revealed an infection rate of 21%; there was a 7% infection rate

when the oral cavity was evaluated.¹⁰⁹ These infection rates are significantly higher than among MSW.^{110,111} In order to prevent SCCA, anal Pap smears can be performed to detect and initiate treatment of AIN, of which grade 2 and 3 are precursors to cancer—although whether the treatment is cost effective has been debated. A 2013 online survey of 18- to 26-year-old men found that only 13% who identified as homosexual or bisexual received at least 1 of the 3 doses required for HPV vaccination.¹¹² Of those who had received the vaccine, 83% were advised to do so by their physician, while 5% of those vaccinated had not discussed it with their physician.¹¹²

HIV and vaccination

HIV-positive patients have less ability to spontaneously resolve the HPV virus from their immune system and have an increased risk of AIN caused by infection.³⁷ HIV is a strong risk factor for the development of SCCA, most of which are associated with HPV type 16.⁵ In addition to increased risk for developing high-grade AIN, patients with HIV have been shown to be coinfecte with multiple HPVs.¹¹³ In Italy, MSM with HIV had a higher likelihood of anal infection with oncogenic HPV types 16 or 18 (80.5%) compared to MSM without HIV (56.0%).⁵⁶ Anal cytologic atypia was also higher in MSM with HIV (46.1% vs 27.9%).⁵⁶ Among MSM with HIV, the rate of infection from oncogenic HPV types of the anus, penis, and oral cavity was 67%, 20%, and 12%, respectively.¹⁰⁹ Women with HIV and associated immunosuppression are at an increased risk of infection from HPV.¹¹⁴

ORGAN TRANSPLANT AND VACCINATION

Key points

- **Organ transplant recipients who are taking immunosuppressant drugs have a decreased ability to clear human papillomavirus infections**
- **Patients who had undergone a liver transplant and who have a higher risk for anal human papillomavirus infection should receive the human papillomavirus vaccine**

Patients taking postorgan transplant immunosuppressant drugs are at increased risk of inability to clear an HPV infection and have a tendency to develop condyloma or cancer.¹¹⁵ Sexually active females who have undergone a renal transplant are at a 10-fold risk for anogenital HPV infection, with risk factors being receptive anal intercourse, duration of immunosuppression, and a history of genital

warts.¹¹⁶ The female renal transplant population is also at a 15-fold higher rate of cervical dysplasia, a 40-fold risk of cervical cancer, and a 100-fold risk of vulvar and anal HPV-induced cancer than the general population.¹¹⁷ Patients who had undergone liver transplants were evaluated within the first 3 weeks postoperatively for anal HPV infection. Eight percent had infections with an oncogenic strain; 10% were infected with nononcogenic HPV types.¹¹⁸ Liver transplant recipients should be tested for oncogenic strains of HPV, be provided the quadrivalent vaccine for those at risk for anal HPV infection, and be annually screened and treated, if positive, for an anal oncogenic HPV infection.¹¹⁸

MANDATORY VACCINATION

Key points

- **Debate exists over mandatory human papillomavirus vaccination**
- **Many feel that human papillomavirus vaccine is unlike other mandatory vaccines because human papillomavirus is spread sexually**

In the United States, state legislators have not often been successful in mandating HPV vaccination for middle school-aged girls, with a legislative pass rate of 27.5%.¹¹⁹ This is because there is local opposition to predication school enrolment to HPV vaccination.¹²⁰ The first state to mandate the vaccine was Texas in 2007 when, by executive order, Governor Rick Perry made HPV vaccination mandatory for girls entering 6th grade, with exceptions for “reasons of conscience, including religious beliefs.” Virginia and the District of Columbia instituted similar requirements.¹²¹ Some lament that mandatory vaccinations interfere with parental autonomy regarding how their child is raised, while others believe that the benefits of herd immunity outweigh parental authority.¹²² The HPV vaccine is dissimilar to other school-mandated vaccines because HPV is sexually transmitted, as opposed to casually transmitted viruses or bacteria, such as polio, measles, or pertussis. Those in favor of mandatory HPV vaccination counter that tetanus is a mandatory vaccination and is a noncommunicable illness. In addition, hepatitis B, whose vaccine is mandated for school entry, is largely a sexually transmitted infection.¹²³ Although opt-out laws exist, many who wish to exercise them find it cumbersome. Proponents have argued that if an exception for vaccination is easy, more parents will wish to opt-out of other vaccination requirements, reducing herd immunity.

PREGNANT WOMEN WITH HUMAN PAPILLOMAVIRUS AND VACCINATION

Key points

- Human papillomavirus is easily transmitted from infected mother to neonate during birth
- The quadrivalent vaccine is category B
- There is no recommendation for the vaccination of pregnant women

Pap testing of the cervix should be performed as part of the prenatal care; 26% to 68% of pregnant women will test positive for HPV infection.¹²⁴⁻¹²⁶ Pregnant women with HPV types 6 and 11—manifesting either subclinically or as genital warts—have a 50% to 70% risk of transferring the virus to the respiratory tract of the neonate during birth via the infected birth canal, which acts as a reservoir, and a 27.3% risk if delivery is via cesarean section, where the neonate may swallow infected amniotic fluid or maternal blood.¹²⁵⁻¹²⁷ Vertical transmission to the fetus may result in HPV infection of the nasopharyngeal or oral mucosa, of which 60% may have HPV DNA detectable by 6 months of age and 10% at 3 years of age. Despite this infection, the child will usually be asymptomatic. Transmission of HPV types 6 or 11 may result in juvenile-onset recurrent respiratory papillomatosis, in which a child will develop benign airway-occluding respiratory papillomas requiring surgical removal.¹²⁸ The annual incidence of this rare occurrence is 0.51 to 4 per 100,000 infants.¹²⁹⁻¹³¹ The cost per case of juvenile-onset recurrent respiratory papillomatosis ranges from \$72,000 and \$387,000.¹²¹

The quadrivalent HPV vaccine does not contain a live virus, so there is no risk of infecting the fetus. The Gardasil package insert states that Gardasil is pregnancy category B, meaning no evidence of female fertility or harm to the fetus, but the manufacturer states that it is not recommended for pregnant women.¹³² During phase III clinical studies, 1796 women became pregnant after receiving the vaccine, yet no anomalies were observed more commonly than in the general population.¹³³ It is not known whether immunizing HPV 6- and 11-infected women will produce antibodies that will cross transplacentally to the fetus and protect from infection of HPV in the genital tract at birth. The bivalent vaccine (Cervarix) is also pregnancy category B, but it is not recommended for pregnant patients unless it is clearly needed.¹³⁴ Gardasil-9 is also not recommended for pregnant women; studies conducted with pregnant rats have not revealed harm to their fetuses, but no well controlled studies have been performed in pregnant humans.¹³⁵

REFERENCES

1. Centers for Disease Control and Prevention website. HPV vaccine information for clinicians—fact sheet. July 8, 2012. Available at: <http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-hcp.htm>. Accessed July 25, 2015.
2. Centers for Disease Control and Prevention website. HPV vaccine—questions & answers. August 6, 2014. Available at: <http://www.cdc.gov/vaccines/vpd-vac/hpv/vac-faqs.htm>. Accessed July 25, 2015.
3. Centers for Disease Control and Prevention website. Incidence, prevalence, and cost of sexually transmitted infections in the United States. Available at: <http://www.cdc.gov/std/stats/STI-Estimates-Fact-Sheet-Feb-2013.pdf>. Access July 25, 2015.
4. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis.* 2013;40:187-193.
5. Schim van der Loeff MF, Mooij SH, Richel O, et al. HPV and anal cancer in HIV-infected individuals: a review. *Curr HIV/AIDS Rep.* 2014;11:250-262.
6. Bertram P, Treutner KH, Rubben A, et al. Invasive squamous-cell carcinoma in giant anorectal condyloma (Buschke-Lowenstein tumor). *Langenbecks Arch Chir.* 1995;380:115-118.
7. Wenzel K, Saka B, Zimmermann R, et al. Malignant conversion of florid oral and labial papillomatosis during topical immunotherapy with imiquimod. *Med Microbiol Immunol.* 2003;192:161-164.
8. Spiniu D, Radulescu A, Bratu O, et al. Giant condyloma acuminatum - Buschke-Lowenstein disease—a literature review. *Chirurgia (Bucur).* 2014;109:445-450.
9. National Cancer Institute website. Human papillomavirus (HPV) vaccines. Available at: <http://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet>. Accessed July 25, 2015.
10. Centers for Disease Control and Prevention. ACIP meeting HPV Luxembourg. Vaccines 2013. Available at: <http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-oct-2013/03-HPV-Luxembourg.pdf>. Published 2013.
11. US Department of Health and Human Services, US Food and Drug Administration website. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm>. Accessed July 25, 2015.
12. US Preventive Services Task Force website. Cervical cancer: screening. Available at: <http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening>. Accessed July 25, 2015.
13. Sankaranarayanan R. Screening for cancer in low- and middle-income countries. *Ann Global Health.* 2014;80:412-417.
14. Downs LS, Smith JS, Scarinci I, Flowers L, Parham G. The disparity of cervical cancer in diverse populations. *Gynecol Oncol.* 2008;109(21 suppl):S22-S30.
15. Ditzian LR, David-West G, Maza M, et al. Cervical cancer screening in low- and middle-income countries. *Mt Sinai J Med.* 2011;78:319-326.
16. Benard VB, Lawson HW, Ehemann CR, Anderson C, Helsel W. Adherence to guidelines for follow-up of low-grade cytologic abnormalities among medically underserved women. *Obstet Gynecol.* 2005;105:1323-1328.
17. Merrill RM, Merrill AV, Mayer LS. Factors associated with no surgery or radiation therapy for invasive cervical cancer in black and white women. *Ethn Dis.* 2000;10:248-256.

18. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012; 30(suppl 5):F12-F23.
19. Centers for Disease Control and Prevention. Genital HPV Infection—Fact Sheet. Human Papillomavirus (HPV): Centers for Disease Control and Prevention; 2014. Available at: <http://www.cdc.gov/std/hpv/hpv-factsheet-march-2014.pdf>. Published January 23, 2014.
20. Hariri S, Unger ER, Sternberg M, et al. Prevalence of genital human papillomavirus among females in the United States, the National Health And Nutrition Examination Survey, 2003-2006. *J Infect Dis*. 2011;204:566-573.
21. Centers for Disease Control and Prevention website. How many cancers are linked with HPV each year? Available at: <http://www.cdc.gov/cancer/hpv/statistics/cases.htm>. Accessed July 22, 2015.
22. Centers for Disease Control and Prevention. Human papillomavirus-associated cancers—United States, 2004-2008. *MMWR Morb Mortal Wkly Rep*. 2012;61:258-261.
23. HPV Center. Human Papillomavirus and Related Diseases Report 2014. Available at: <http://www.hpcentre.net/summary-report.php>. Published December 18, 2014.
24. Goldie SJ, Grima D, Kohli M, et al. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. *Int J Cancer*. 2003;106:896-904.
25. Duenas-Gonzalez A, Serrano-Olvera A, Cetina L, Coronel J. New molecular targets against cervical cancer. *Int J Women's Health*. 2014;6:1023-1031.
26. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356:1944-1956.
27. Hammarstedt L, Lindquist D, Dahlstrand H, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer*. 2006;119:2620-2623.
28. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29:4294-4301.
29. Franceschi S, Bidoli E, Herrero R, Munoz N. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral Oncol*. 2000;36:106-115.
30. Hernandez BY, Goodman MT, Lynch CF, et al. Human papillomavirus prevalence in invasive laryngeal cancer in the United States. *PloS One*. 2014;9:e115931.
31. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol*. 2012;13:607-615.
32. Gillison ML. Human papillomavirus-related diseases: oropharynx cancers and potential implications for adolescent HPV vaccination. *J Adolesc Health*. 2008;43:S52-S60.
33. Kansy K, Thiele O, Freier K. The role of human papillomavirus in oral squamous cell carcinoma: myth and reality. *Oral Maxillofac Surg*. 2014;18:165-172.
34. Strojan P, Zadnik V, Sifrer R, et al. Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983-2009: role of human papillomavirus infection. *Eur Arch Otorhinolaryngol*. doi: <http://dx.doi.org/10.1007/s00405-014-3459-7>. Published online December 27, 2014.
35. Joseph DA, Miller JW, Wu X, et al. Understanding the burden of human papillomavirus-associated anal cancers in the US. *Cancer*. 2008;113:2892-2900.
36. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124:1626-1636.
37. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine*. 2012;30(suppl 5):F24-F33.
38. Prendes BL, Wang SJ, Groppo ER, Eisele DW, Palefsky JM. Oral human papillomavirus infection in men who have sex with men with anal squamous intraepithelial lesions. *Head Neck*. <http://dx.doi.org/10.1002/hed.24006>. Published online January 12, 2015.
39. Mendez-Martinez R, Rivera-Martinez NE, Crabtree-Ramirez B, et al. Multiple human papillomavirus infections are highly prevalent in the anal canal of human immunodeficiency virus-positive men who have sex with men. *BMC Infect Dis*. 2014;14:671.
40. Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol*. 2012;13:487-500.
41. Hartwig S, Syrjanen S, Dominiak-Felden G, Brotons M, Castellsague X. Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review. *BMC Cancer*. 2012;12:30.
42. Hsueh PR. Human papillomavirus, genital warts, and vaccines. *J Microbiol Immunol Infect*. 2009;42:101-106.
43. Kraut AA, Schink T, Schulze-Rath R, Mikolajczyk RT, Garbe E. Incidence of anogenital warts in Germany: a population-based cohort study. *BMC Infect Dis*. 2010;10:360.
44. Castellsague X, Cohet C, Puig-Tintore LM, et al. Epidemiology and cost of treatment of genital warts in Spain. *Eur J Public Health*. 2009;19:106-110.
45. Kliewer EV, Demers AA, Elliott L, Lotocki R, Butler JR, Brisson M. Twenty-year trends in the incidence and prevalence of diagnosed anogenital warts in Canada. *Sex Transm Dis*. 2009;36:380-386.
46. Marra F, Ogilvie G, Colley L, Kliewer E, Marra CA. Epidemiology and costs associated with genital warts in Canada. *Sex Transm Infect*. 2009;85:111-115.
47. de Sanjose S, Bruni L, Alemany L. HPV in genital cancers (at the exception of cervical cancer) and anal cancers. *Presse Med*. 2014;43:e423-e428.
48. Feber A, Arya M, de Winter P, et al. Epigenetics markers of metastasis and HPV-induced tumorigenesis in penile cancer. *Clin Cancer Res*. 2015;21:1196-1206.
49. Hernandez BY, Goodman MT, Unger ER, et al. Human papillomavirus genotype prevalence in invasive penile cancers from a registry-based United States population. *Front Oncol*. 2014;4:9.
50. Miralles-Guri C, Bruni L, Cubilla AL, Castellsague X, Bosch FX, de Sanjose S. Human papillomavirus prevalence and type distribution in penile carcinoma. *J Clin Pathol*. 2009;62:870-878.
51. Kalantari M, Villa LL, Calleja-Macias IE, Bernard HU. Human papillomavirus-16 and -18 in penile carcinomas: DNA methylation, chromosomal recombination and genomic variation. *Int J Cancer*. 2008;123:1832-1840.
52. Kahn JA, Lan D, Kahn RS. Sociodemographic factors associated with high-risk human papillomavirus infection. *Obstet Gynecol*. 2007;110:87-95.
53. Dahlstrom KR, Burchell AN, Ramanakumar AV, et al. Sexual Transmission of Oral Human Papillomavirus Infection among Men. *Cancer Epidemiol Biomarkers Prev*. 2014;23:2959-2964.
54. Cook RL, Thompson EL, Kelso NE, et al. Sexual behaviors and other risk factors for oral human papillomavirus infections in young women. *Sex Transm Dis*. 2014;41:486-492.

55. Widdice L, Ma Y, Jonte J, et al. Concordance and transmission of human papillomavirus within heterosexual couples observed over short intervals. *J Infect Dis.* 2013;207:1286-1294.
56. Latini A, Dona MG, Ronchetti L, et al. Prevalence of anal human papillomavirus infection and cytologic abnormalities among HIV-infected and HIV-uninfected men who have sex with men. *J Int AIDS Soc.* 2014;17:19662.
57. Richel O, De Vries HJ, Dijkgraaf MG, Van Noesel CJ, Prins JM. Risk Factors for the presence of anal intraepithelial neoplasia in HIV+ men who have sex with men. *PLoS One.* 2013;8:e84030.
58. American Cancer Society. Do we know what causes anal cancer? *Anal Cancer* 2014. Available at: <http://www.cancer.org/cancer/analcancer/detailedguide/anal-cancer-what-causes>. Published May 2, 2014.
59. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine.* 2006;24(Suppl 3). S3/35-41.
60. Korostil IA, Regan DG. The potential impact of HPV-16 reactivation on prevalence in older Australians. *BMC Infect Dis.* 2014;14:312.
61. National Cancer Institute. HPV and Cancer. Cancer Topics 2012. Available at: <http://www.cancer.gov/cancertopics/factsheet/Risk/HPV#r1>. Published March 15, 2012.
62. Niederhuber JE, Armitage JO, Doroshow JH, Kastan MB, Tepper JE, Abeloff MD. *Abeloff's clinical oncology*. Philadelphia (PA): Elsevier; 2014.
63. Bernard HU. Gene expression of genital human papillomaviruses and considerations on potential antiviral approaches. *Antivir Ther.* 2002;7:219-237.
64. Zhou J, Sun XY, Louis K, Frazer IH. Interaction of human papillomavirus (HPV) type 16 capsid proteins with HPV DNA requires an intact L2 N-terminal sequence. *J Virol.* 1994;68:619-625.
65. Wang JW, Jagu S, Wang C, et al. Measurement of neutralizing serum antibodies of patients vaccinated with human papillomavirus L1 or L2-based immunogens using furin-cleaved HPV Pseudovirions. *PLoS One.* 2014;9:e101576.
66. Beltrao M, Wanderley MS, de Santana NA, Bruneska D, de Lima Filho JL. Site of infections associated with human papillomavirus. *Arch Gynecol Obstet.* 2014.
67. Stubenrauch F, Laimins LA. Human papillomavirus life cycle: active and latent phases. *Semin Cancer Biol.* 1999;9:379-386.
68. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. *Cell.* 1993;75:495-505.
69. Duensing S, Munger K. Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. *Int J Cancer.* 2004;109:157-162.
70. Almeida AM, Queiroz JA, Sousa F, Sousa A. Optimization of supercoiled HPV-16 E6/E7 plasmid DNA purification with arginine monolith using design of experiments. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2014;978-979:145-150.
71. Sahiner F. [Current problems and recent advances in the molecular diagnosis of genital human papillomavirus infections]. *Mikrobiyol Bul.* 2014;48:689-706.
72. Smith JA, Haberstroh FS, White EA, Livingston DM, DeCaprio JA, Howley PM. SMCX and components of the TIP60 complex contribute to E2 regulation of the HPV E6/E7 promoter. *Virology.* 2014;468-470:311-321.
73. Malejczyk M, Jozwiak J, Osiecka A, et al. Serum levels of soluble tumor-necrosis-factor receptors in patients with benign and malignant HPV-associated anogenital lesions. *Int J Cancer.* 1997;73:16-19.
74. Dochez C, Bogers JJ, Verhelst R, Rees H. HPV vaccines to prevent cervical cancer and genital warts: an update. *Vaccine.* 2014;32:1595-1601.
75. Szarewski A. Cervarix(R): a bivalent vaccine against HPV types 16 and 18, with cross-protection against other high-risk HPV types. *Expert Rev Vaccines.* 2012;11:645-657.
76. Papadopoulos AJ, Schwartz RA, Lefkowitz A, Tinkle LL, Janniger CK, Lambert WC. Extranodal Bowenoid papulosis associated with atypical human papillomavirus genotypes. *J Cutan Med Surg.* 2002;6:117-121.
77. Grimes RM, Benjamins LJ, Williams KL. Counseling about the HPV vaccine: desexualize, educate, and advocate. *J Pediatr Adolesc Gynecol.* 2013;26:243-248.
78. Goldstone SE, Jessen H, Palefsky JM, et al. Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males. *Vaccine.* 2013;31:3849-3855.
79. Hillman RJ, Giuliano AR, Palefsky JM, et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. *Clin Vaccine Immunol.* 2012;19:261-267.
80. Administration UFaD. FDA: Gardasil approved to prevent anal cancer. In: S. Burgess editor. News & Events. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237941.htm>. Accessed August 6, 2015.
81. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *New Engl J Med.* 2011;365:1576-1585.
82. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *New Engl J Med.* 2011;364:401-411.
83. Merck. Patient Information about GARDASIL®92014. Available at: http://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_ppi.pdf. Published December 10, 2014.
84. Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol.* 2006;2006(suppl):40470.
85. Burger RA, Monk BJ, Kurosaki T, et al. Human papillomavirus type 18: association with poor prognosis in early stage cervical cancer. *J Natl Cancer Inst.* 1996;88:1361-1368.
86. Hariri S, Unger ER, Schafer S, et al. HPV type attribution in high grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States. *Cancer Epidemiol Biomarkers Prev.* 2015;24:393-399.
87. Administration UFaD. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. FDA News Release FDA; 2014. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm>. Published December 10, 2014.
88. Stern PL, van der Burg SH, Hampson IN, et al. Therapy of human papillomavirus-related disease. *Vaccine.* 2012;30(suppl 5):F71-F82.
89. Stanley MA, Sudenga SL, Giuliano AR. Alternative dosage schedules with HPV virus-like particle vaccines. *Exp Rev Vaccines.* 2014;13:1027-1038.
90. Jit M, Brisson M, Laprise JF, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. *BMJ.* 2015;350:g7584.
91. Sante et Services Sociaux Quebec. Human Papillomavirus Viruses (HPV): Quebec; 2013.

92. NHS England. *Change in schedule from three to two doses in the HPV vaccination programme*. England: Public Health England; 2014.
93. Waller J, Marlow LA, Wardle J. Mothers' attitudes towards preventing cervical cancer through human papillomavirus vaccination: a qualitative study. *Cancer Epidemiol Biomarkers Prev*. 2006;15:1257-1261.
94. Bednarczyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics*. 2012;130:798-805.
95. Kann L, Kinchen S, Shanklin SL, et al. Youth risk behavior surveillance—United States, 2013. *MMWR Surveill Summ*. 2014;63(suppl 4):1-168.
96. Institute of Education Sciences website. Trends in the prevalence of selected risk behaviors and obesity for all students national YRBS: 1991-2011. Available at: <http://files.eric.ed.gov/fulltext/ED532809.pdf>. Accessed July 25, 2015.
97. Liddon NC, Leichliter JS, Markowitz LE. Human papillomavirus vaccine and sexual behavior among adolescent and young women. *Am J Prev Med*. 2012;42:44-52.
98. Mayhew A, Mullins TL, Ding L, et al. Risk perceptions and subsequent sexual behaviors after HPV vaccination in adolescents. *Pediatrics*. 2014;133:404-411.
99. Taylor LD, Hariri S, Sternberg M, Dunne EF, Markowitz LE. Human papillomavirus vaccine coverage in the United States, National Health and Nutrition Examination Survey, 2007-2008. *Prev Med*. 2011;52:398-400.
100. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, et al. Age of sexual debut among US adolescents. *Contraception*. 2009;80:158-162.
101. Baxter CE, Barata PC. The paradox of HPV vaccines: how to reach sexually inexperienced women for protection against a sexually transmitted infection. *Womens Health Issues*. 2011;21:239-245.
102. Winer RL, Lee SK, Hughes JP, et al. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157:218-226.
103. Munoz N, Manalastas R Jr, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. *Lancet*. 2009;373:1949-1957.
104. Baron J, Beresford P, Gould J, Patel K, Nash P, Freer M. Time to vaccinate boys against HPV infection and cancer, say parliamentarians with special interest in public health. *BMJ*. 2014;349:g5789.
105. Tian LH, Peterman TA, Tao G, et al. Heterosexual anal sex activity in the year after an STD clinic visit. *Sex Transm Dis*. 2008;35:905-909.
106. Nyitray AG, da Silva RJ, Baggio ML, et al. The prevalence of genital HPV and factors associated with oncogenic HPV among men having sex with men and men having sex with women and men: the HIM study. *Sex Transm Dis*. 2011;38:932-940.
107. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst*. 1995;87:796-802.
108. Karnes JB, Usatine RP. Management of external genital warts. *Am Fam Physician*. 2014;90:312-318.
109. van Rijn VM, Mooij SH, Mollers M, et al. Anal, penile, and oral high-risk HPV infections and HPV seropositivity in HIV-positive and HIV-negative men who have sex with men. *PLoS One*. 2014;9:e92208.
110. Vardas E, Giuliano AR, Goldstone S, et al. External genital human papillomavirus prevalence and associated factors among heterosexual men on 5 continents. *J Infect Dis*. 2011;203:58-65.
111. Nicolau SM, Camargo CG, Stavale JN, et al. Human papillomavirus DNA detection in male sexual partners of women with genital human papillomavirus infection. *Urology*. 2005;65:251-255.
112. Reiter PL, McRee AL, Katz ML, Paskett ED. Human papillomavirus vaccination among young adult gay and bisexual men in the United States. *Am J Public Health*. 2015;105:96-102.
113. Strickler HD, Palefsky JM, Shah KV, et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. *J Natl Cancer Inst*. 2003;95:1062-1071.
114. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. 2014;59:127-135.
115. Forcier M, Musacchio N. An overview of human papillomavirus infection for the dermatologist: disease, diagnosis, management, and prevention. *Dermatol Ther*. 2010;23:458-476.
116. Patel HS, Silver AR, Levine T, Williams G, Northover JM. Human papillomavirus infection and anal dysplasia in renal transplant recipients. *Br J Surg*. 2010;97:1716-1721.
117. Sillman FH, Sentovich S, Shaffer D. Ano-genital neoplasia in renal transplant patients. *Ann Transplant*. 1997;2:59-66.
118. Grat M, Grat K, Hołówko W, et al. Initial prevalence of anal human papilloma virus infection in liver transplant recipients. *Transpl Int*. 2014;27:816-823.
119. Laugesen MJ, Mistry R, Carameli KA, Ribisl KM, Needleman J, Bastani R. Early policy responses to the human papillomavirus vaccine in the United States, 2006-2010. *J Adolesc Health*. 2014;55:659-664.
120. Haber G, Malow RM, Zimet GD. The HPV vaccine mandate controversy. *J Pediatr Adolesc Gynecol*. 2007;20:325-331.
121. Casciotti DM, Smith KC, Andon L, Vernick J, Tsui A, Klassen AC. Print news coverage of school-based human papillomavirus vaccine mandates. *J School Health*. 2014;84:71-81.
122. Colgrove J. The ethics and politics of compulsory HPV vaccination. *N Engl J Med*. 2006;355:2389-2391.
123. Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States, 1982-1998: implications for vaccination programs. *J Infect Dis*. 2002;185:713-719.
124. Bandyopadhyay S, Chatterjee R. HPV viral load determination during pregnancy as a possible cervical cancer risk. *J Exp Clin Cancer Res*. 2006;25:29-38.
125. Gajewska M, Wielgos M, Kaminski P, et al. The occurrence of genital types of human papillomavirus in normal pregnancy and in pregnant renal transplant recipients. *Neuroendocrinol Lett*. 2006;27:529-534.
126. Gajewska M, Marianowski L, Wielgos M, Malejczyk M, Majewski S. The occurrence of genital types of human papillomavirus in normal pregnancy and in pregnant women with pregestational insulin dependent diabetes mellitus. *Neuroendocrinol Lett*. 2005;26:766-770.
127. Tseng CJ, Liang CC, Soong YK, Pao CC. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol*. 1998;91:92-96.
128. Gallagher TQ, Derkay CS. Recurrent respiratory papillomatosis: update 2008. *Curr Opin Otolaryngol Head Neck Surg*. 2008;16:536-542.

129. Shah KV. A case for immunization of human papillomavirus (HPV) 6/11-infected pregnant women with the quadrivalent HPV vaccine to prevent juvenile-onset laryngeal papilloma. *J Infect Dis.* 2014;209:1307-1309.
130. Marsico M, Mehta V, Chastek B, Liaw KL, Derkay C. Estimating the incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis in publicly and privately insured claims databases in the United States. *Sex Transm Dis.* 2014;41:300-305.
131. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine.* 2012;30:6016-6019.
132. *Gardasil [package insert].* Kenilworth (NJ): Merck and Co; 2011.
133. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol.* 2009;114:1179-1188.
134. *Cervarix [package insert].* New York (NY): GlaxoSmithKline; 2009.
135. Merck & Co. Merck's Investigational 9-valent HPV Vaccine, V503, Prevented 97 Percent of Cervical, Vaginal and Vulvar Pre-cancers Caused by Five Additional HPV Types, in Phase III Study 2013.

Human papillomavirus vaccine trials and tribulations

Vaccine efficacy

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Learning objectives

After completing this learning activity, participants should be able to identify the timeframe for efficacy of the human papilloma virus vaccines currently available; list the human papilloma virus vaccines recommended for various patient populations; and discuss study data comparing the cost effectiveness of human papilloma virus vaccinations in the United States.

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As of December 2014, there were 3 approved vaccines for human papillomavirus (HPV): bivalent Cervarix (GlaxoSmithKline, New York, NY), quadrivalent Gardasil (Merck and Co, Kenilworth, NJ), and 9-valent Gardasil-9 (Merck and Co). The average cost per dose is \$120, with a recommended 3-dose course. The quadrivalent vaccine is the most widely administered worldwide. As with the bivalent and 9-valent vaccines, the vaccine is considered safe, although concerns have been raised. In addition to immunization against the targeted HPV types, there is evidence that there is cross protection against other types of HPV. This continuing medical education review evaluates the differences in vaccines that are currently on the market; part II focuses on the cost-effectiveness of vaccination, the HPV vaccination programs currently instituted around the globe, efficacy, and safety. (J Am Acad Dermatol 2015;73:759-67.)

Key words: anal cancer; Cervarix; cervical cancer; condylomas; Gardasil; human papillomavirus; vaccine.

INTRODUCTION

Key points

- **The quadrivalent human papillomavirus vaccine is recommended for both boys and girls**
- **The bivalent human papillomavirus vaccine is recommended for girls only**
- **The 9-valent human papillomavirus vaccine is recommended for both boys and girls**

The current recommendation by the Advisory Committee on Immunization Practices (ACIP) for human papillomavirus (HPV) vaccine dosing is for females to receive either the bivalent HPV or quadrivalent HPV vaccine at 11 or 12 years of age; males are approved only to receive the quadrivalent HPV vaccine at 11 or 12 years of age.¹ The 9-valent vaccine has been approved by the US Food and Drug Administration (FDA) for

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Abbreviations used:

ACA:	Affordable Care Act
ACIP:	Advisory Committee on Immunization Practices
AIN:	anal intraepithelial neoplasia
CDC:	Centers for Disease Control and Prevention
CHMP:	European Committee for Medicinal Products for Human Use
CIN:	cervical intraepithelial neoplasia
FDA:	US Food and Drug Administration
HPV:	human papillomavirus
ICER:	incremental cost-effectiveness ratio
MSM:	men who have sex with men
MSW:	men who have sex with women
OPSCC:	oropharyngeal squamous cell carcinoma
QALY:	quality-adjusted life year
VLP:	virus-like particle

females 9 to 26 years of age, but the vaccine has not yet been added to the ACIP dosing schedule (**Table I**). Females are also recommended to receive the vaccine between 13 and 26 years of age and males between 13 and 21 years of age if they have not been vaccinated previously. The ACIP also recommends vaccination of men who have sex with men (MSM) and those who are immunocompromised up to 26 years of age even if they have not been vaccinated previously.¹ With a per-dose cost of \$120, health care payers must decide whether expenditures for HPV vaccination are cost-effective. Diagnoses of HPV-associated cancers averaged 26,900 per year between the years 2004 and 2008 in the United States—of which approximately 4100 women die of cervical cancer.³⁻⁵ Although screening frequency for cervical cancer is similar, the highest risk for cervical cancer is among nonEnglish speakers, Hispanics, and black women, primarily due to poor follow-up.⁶ Studies following recipients of the HPV vaccine have shown that vaccination rates are lowest among urban black and Hispanic women as well as all people of low socioeconomic status.

Vaccine differences

There are currently 3 licensed HPV vaccines in the United States. All are composed of type-specific HPV L1 protein. The bivalent HPV vaccine has 2 noninfectious virus-like particles (VLPs); the quadrivalent HPV vaccine has 4 VLPs and the 9-valent HPV vaccine has 9 VLPs. The Centers for Disease Control and Prevention (CDC) has made recommendations for use of the bivalent, quadrivalent, and 9-valent vaccines⁷ (**Table I**). The 9-valent vaccine has shown equal efficacy in women 16 to 26 years of age when compared to the quadrivalent vaccine.⁸ In

addition, it has shown efficacy against the additional 5 HPV types at a rate of 97.1%.⁹

VACCINATION COST-EFFECTIVENESS**Key points**

- In the United States, \$6.8 billion is spent annually on cervical dysplasia screening
- If female human papillomavirus vaccination rates rise above 75%, it is not cost effective to vaccinate males
- The cost per quality-adjusted life year could be reduced if women were vaccinated and human papillomavirus cytology screening was reduced from every 3 to 5 years
- The incremental cost ratio of providing men who have sex with men the quadrivalent human papillomavirus vaccine before 27 years of age is \$87,240 per quality-adjusted life year

As a result of the novelty of the vaccine being so new, the rate of reduction of HPV-related cancers is unknown.¹⁰ The cost to vaccinate an individual with a 3-shot course of either the bivalent or quadrivalent vaccine is between \$350 and \$500.¹¹ Roughly 55 million cervical Papanicolaou (Pap) smears are performed annually in the United States, at an average cost of \$103 per screening, totaling \$5.67 billion.¹²⁻¹⁴ The cost for follow-up of Pap smears—including false positives and cervical intraepithelial neoplasia (CIN)—is \$1.2 billion annually.¹⁵ More than \$1 billion is spent annually on the treatment of genital warts, cervical cancer, and oropharyngeal cancers combined¹⁶ (**Table II**). Via mathematical models, the most cost-effective immunization technique to prevent cervical cancer is to vaccinate all females, and not males, because females are at the highest prevalence of HPV complications from infection.¹⁷ Although HPV infections and cervical cancer are higher among unmarried, low-income black women, with low education, cost-effectiveness studies have not been performed on immunizing individuals based on income, education, or race.¹⁸ Because of the lower incidence of anal, penile, and oropharyngeal cancer in males—compared to the incidence of HPV-induced cancers in women—the cost-effectiveness of vaccinating males is diminished.¹⁹

Disease burden, which encompasses both quantity and quality of life lived, is measured by quality-adjusted life year (QALY), where a perfect health year is valued at 1.0 and death is valued at 0.0. Measurement in QALYs is used to determine the value for money of intervention, with a lower cost to QALY gained, known as incremental cost effectiveness ratio (ICER), preferred. If the female vaccination rate remains low (ie, <30% by 12 years of age) and

Table I. Human papillomavirus vaccines and recommendations in the United States²

Recommendations	Gardasil*	Cervarix†	Gardasil-9*
Advisory Committee on Immunization Practices recommendations	<ul style="list-style-type: none"> 11- or 12-year-old girls 11- or 12-year-old boys 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccination series Males 22-26 years of age may be vaccinated MSM and MSWM and immunocompromised patients 22-26 years of age Delivered through 3 intramuscular injections over a 6-month period The second and third doses should be given 2 and 6 months after the first dose 	<ul style="list-style-type: none"> 11- or 12-year-old girls 13- to 26-year-old females if have not completed vaccination series 	<ul style="list-style-type: none"> 11- or 12-year-old girls 11- or 12-year-old boys 13- through 26-year-old females and 13- through 21-year-old males who have not completed the vaccination series MSM and MSWM and immunocompromised patients up to 26 years of age
HPV vaccine administration		<ul style="list-style-type: none"> Delivered through 3 intramuscular injections over a 6-month period The second and third doses should be given 2 and 6 months after the first dose 	<ul style="list-style-type: none"> Delivered through 3 intramuscular injections over a 6-month period The second and third doses should be given 2 and 6 months after the first dose

FDA, US Food and Drug Administration; MSM, men who have sex with men; MSWM, men who have sex with both women and men.

*Gardasil and Gardasil 9 are trademarks of Merck and Co (Kenilworth, NJ).

†Cervarix is a trademark of GlaxoSmithKline (New York, NY).

Table II. Annual cost of treatment by cancer or tumor type¹⁶

Cancer or tumor type	Cost (in millions, USD)
Cervical cancer	\$441
Oropharyngeal cancer	\$306
Genital warts	\$288

the cost of treatment of benign genital warts is ignored, then it is cost-effective to treat males, with a cost per QALY gained by male vaccination of <\$50,000.¹⁹ However, if female HPV vaccination rates rise to 75%, it is not cost-effective to immunize males as long as genital warts are not considered, because the cost per QALY would be >\$100,000.¹⁹ The cost to perform HPV and cytology testing for HPV in women every 3 years beginning at 21 years of age is \$78,000 per QALY.²⁰ If HPV cytology screening were reduced in HPV-vaccinated women from every 3 years to every 5 years, then the cost per year would be \$41,000 per QALY.²⁰ Similar findings were seen in reports from Spain.²¹ Annual Pap smears in women with HIV and CD4 counts <200 cells/mm³ have an ICER of \$112,026, well above the ceiling that is considered cost-effective.²²

Although advocated by many, routine anal intraepithelial neoplasia (AIN) screening for MSM is debated.²³ No evidential basis for screening is available because the use of a control group—which would not receive intervention compared to a group receiving

screening and intervention—may not be ethical.²³ An ICER of <\$30,000 to \$50,000, a level considered cost-effective, is seen in performing Pap smears on men with HIV (\$16,600) or all HIV-negative MSM every 3 years (\$7800).²⁴⁻²⁶ For the prevention of anal cancers, of which MSM are at enhanced risk, it is cost-effective to vaccinate MSM up to age 26 years of age.²⁷ In MSM who are HIV-negative, the lifetime risk of anal cancer, which is 5.1 per 100,000 person-years, was reduced by 60.77% with vaccination, creating an ICER of \$87,240 per QALY, if patients are vaccinated before 27 years of age.²⁸

Several countries have recently changed from a 3-to 2-dose immunization schedule to reduce the cost of immunization. Using two doses is a cost-effective strategy if the immunization provides lifelong immunity. If not, providing the third dose is more cost-effective, even if the 2-dose schedule provides 30 years of immunity.²⁹

COVERAGE FOR VACCINATION

Key points

- The majority of developed countries have vaccination programs for girls
- International aid organizations are working with developing nations to develop human papillomavirus vaccination programs

In the United States, the quadrivalent HPV vaccine is currently approved by the FDA for males and females 9 to 26 years of age, the bivalent vaccine for females 9 to 25 years of age, and the 9-valent vaccine for females 9

Table III. Immunizations provided

Group immunized	Regions/countries that provide free vaccination	Vaccine	Miscellaneous
Girls 9-13 years of age	Africa: Ghana, Kenya, Madagascar, Malawi, Niger, Sierra Leone, Tanzania, and South Africa	Quadrivalent	Financially supported by international aid organization; South Africa: income-based payment
Australia: Girls and boys 12-13 years of age and boys 14-15 years of age if not Vaccinated; New Zealand: girls in 8th grade	Australasia: Australia and New Zealand	Quadrivalent	
Girls; age varies by province/territory	Canada	Quadrivalent	Recommendation set by province/territory
Austria: recommends both boy and girls be immunized	Central Europe		Paid by patient, including Austria
Girls	Middle and Eastern Europe: Hungary, Bulgaria, Czech Republic, Latvia, Romania, Slovenia, and Macedonia, Greece	Quadrivalent	Other Middle and Eastern European countries; paid by patient
Girls	Western Europe: Italy, Germany, Denmark, United Kingdom, Portugal, Netherlands, Spain, and Switzerland		
Girls	Middle East: Israel		School-based program
Girls—Mexico: 9 years of age/Panama: 10 years of age	Central America: Mexico and Panama		Mexico has not fully implemented its program
Girls—South Korea: females 9-26 years of age and males 9-15 years of age	Asia: Laos and South Korea	Quadrivalent	Laos program financially supported by international aid organization
Girls 9-26 years of age	Caribbean: Trinidad and Tobago		
Girls and boys	United States	Bivalent or quadrivalent	See Table I for dosing schedule

to 26 years of age and males 9 to 15 years of age. The European Committee for Medicinal Products for Human Use (CHMP) has approved the quadrivalent vaccine for all people ≥ 9 years of age³⁰ and the bivalent vaccine for females ≥ 9 years of age.³¹ The CHMP has not yet approved the 9-valent HPV vaccine. In 2014, the CHMP approved a 2-dose, rather than a 3-dose, immunization schedule for boys and girls 9 to 13 years of age.³² Payment for the vaccination varies by country; coverage may change depending on laws and modifications in the recommended vaccination schedule. When the legislation was written, the Affordable Care Act of 2010 (ACA) dictated that private insurance companies provide—at no additional cost to the recipient—immunizations recommended by the ACIP. At that time, the recommendation was for the quadrivalent HPV vaccine in females.³³ However, in 2011, the CDC also began recommending the quadrivalent vaccination for males.³⁴ HPV vaccines for those without insurance are currently provided at no charge through the CDC program Vaccines for Children,

which provides coverage for boys and girls who are Medicaid eligible, American Indian, Alaska Native, or uninsured and who are ≤ 19 years of age for either the bivalent or quadrivalent HPV vaccine.¹ Starting in 2014, health plans on the health insurance exchanges must also provide ACIP-recommended vaccinations at no cost to beneficiaries.³⁵ The lowest immunization rates in the United States are currently among low-income groups.³⁶

An ever-increasing number of countries are integrating HPV vaccinations into their national health programs (Table III).^{37,38} With the exception of income-based payment in South Africa,³⁹ some African nations are starting vaccinations with the assistance of aid organizations⁴⁰ (Fig 1). Australia vaccinates both boys and girls.⁴¹ In Canada, each province and territory has decided to provide HPV vaccination to select groups, the earliest being in 4th grade but the majority vaccinating in the 6th grade.⁴²⁻⁴⁵ In Europe, Austria is the only country that recommends that both boys and girls be vaccinated.⁴⁶ In

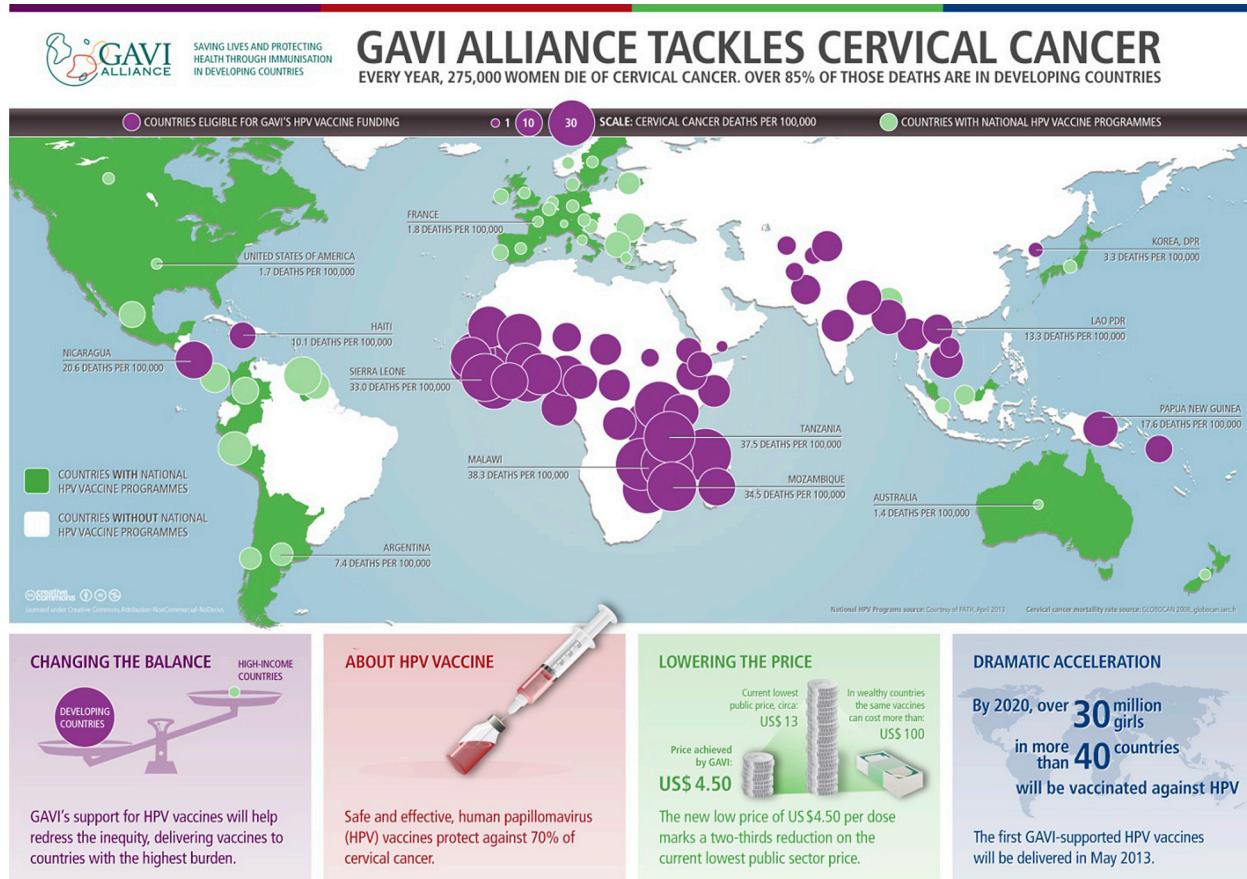


Fig 1. Human papillomavirus mortality caused by cervical cancer and countries with immunization programs. (Map provided by the GAVI Alliance.⁴⁰ Reproduced with permission.)

many countries in Central and Eastern Europe, the cost of vaccination is paid by the patient, with few exceptions. There are an increasing number of countries in Western Europe where HPV vaccination is provided at no cost via school-based programs or covered by the national health agency at health clinics.^{47,48} Israel has established a school-based immunization program for HPV immunization of girls.⁴⁹ Central America has only a few nations vaccinating.⁵⁰ In Asia, Laos is beginning immunization for girls with assistance from an international aid organization⁴⁰; South Korea has a quadrivalent vaccination program for girls 9 to 26 years of age and boys 9 to 15 years of age.⁵⁰ In the Caribbean, only Trinidad and Tobago have free HPV immunization. In 2013, Japan ceased its nationally funded HPV vaccination program because of concerns of the development of complex regional pain syndrome, a painful swelling of the extremities.⁵¹

VACCINE SAFETY

Key points

- No study has found an increased risk of demyelinating disease as compared to the general population

- In 2013, Japan ceased its national human papillomavirus immunization program due to fears of adverse reactions

More than 175 million doses of the quadrivalent vaccine have been given worldwide.⁵² There has been concern that vaccination has led to an increase in multiple sclerosis, optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica.⁵³⁻⁵⁵ A 2015 Danish study evaluated almost 4 million females and found no increased risk for the development of multiple sclerosis or other central nervous system demyelinating disease.⁵⁶ In 2013, Japan suspended its vaccination program after concerns of complex regional pain syndrome.⁵¹ Ten cases of complex regional pain syndrome have been reported in patients after receiving the HPV vaccine.⁵⁷ As of July 2013, the CDC has received 4 reports of premature ovarian failure, possibly caused by an autoimmune reaction triggered by the vaccine.^{57,58} The CDC has found no causality between the quadrivalent HPV vaccine and complex regional pain syndrome or premature ovarian failure. Studies of the bivalent vaccine have not found any increased risk of development of

serious adverse events.⁵⁹⁻⁶¹ The most common side effects included injection site pain, reported in up to 50% of recipients, and mild fever and injection site reaction after the first dose in 10% to 50% of those receiving the vaccine.^{30,59} The vaccines have shown efficacy with an allergic side effect risk similar to other vaccines. The CDC states that few adverse events have been reported with immunization. Regarding the quadrivalent vaccine, 94% of reported adverse events include syncope, local reaction, dizziness, nausea, and headache.^{62,63}

WHICH VACCINE IS MOST EFFICACIOUS?

Key points

- Both the bivalent and quadrivalent vaccines are efficacious for at least 10 years
- The Centers for Disease Control and Prevention is monitoring vaccinated patients for both efficacy and side effects
- No booster vaccine is currently recommended

Both the quadrivalent and bivalent vaccines are efficacious against their respective HPV types.⁶⁴⁻⁶⁹ In addition, both have some cross-protection against HPV types that are not targeted by the vaccine.^{65,68,70,71} The bivalent vaccine has more cross-protection against oncogenic HPV types in addition to types 16 and 18 than does the quadrivalent vaccine.⁷⁰⁻⁷³ The bivalent vaccine provides cross-neutralization to HPV type 31, while the quadrivalent does not.⁷⁴ Both the quadrivalent and bivalent vaccines have similar antibody titers to nonvaccine HPV types 31, 33, and 45.⁷⁵ The bivalent vaccine has slightly higher rates of CD4⁺ cytokine response against 4 tested HPV types (ie, 16, 18, 33, and 45), but the clinical correlation with disease prevention is uncertain.⁷⁴ The bivalent vaccine has higher anti-HPV type 16 and anti-HPV type 18 antibodies and neutralization titers 7 months after vaccination compared to the quadrivalent vaccine.⁷⁴ Avidity of antibodies is similar between the 2 vaccines.⁷⁴ Because of cross-protection against HPV types 31, 33, and 45—in addition to protection against HPV types 16 and 18—cervical cancer incidence may be reduced to 9.5 cases per 1000 patients with the bivalent vaccine compared to estimated 14 cases per 100,000 patients with the quadrivalent vaccine.⁷⁶ It is known that postvaccination protection from the bivalent vaccine lasts at least 9.4 years.⁷⁶ With similar immunization costs but a lower anticipated prevalence of cervical cancer, the bivalent vaccine may be more cost-effective.^{7,74,77,78} The CDC states that both the bivalent and quadrivalent vaccines maintain efficacy for at least 10 years based on ongoing research.⁷⁹ Currently, the ACIP is monitoring both

vaccines for safety and efficacy and states that no booster dose for either vaccine is recommended.⁷⁹

WILL AN INCREASE IN VACCINATION CAUSE A SPIKE IN OTHER HUMAN PAPILLOMAVIRUS SUBTYPES?

Key point

- It is unknown if vaccination will lead to a change in prevalence of human papillomavirus genotypes

With an increase in vaccination with quadrivalent and bivalent HPV vaccines, other HPV types will remain. In 2007, Australia began a national campaign to vaccinate all school-aged girls with the quadrivalent HPV vaccine; as of 2011, they had vaccinated 73% of all school-aged girls.⁸⁰ Of those in the age group that had been targeted for quadrivalent vaccination before they began sexual activity, no cases of HPV types 6, 11, or 18 were identified on HPV DNA vaginal swabs. The prevalence of HPV type 16 was 1.6%, although the study could not determine whether these were in women who were vaccinated or not. The rates of HPV types not included in the quadrivalent vaccine—including types 51, 59, 73, 84, and 89—were more prevalent in the cohort (3.9% prevalence for each).⁸¹ The authors noted that the rate of HPV type 16 was 18% before vaccinations began.⁸² The addition of the 9-valent vaccine will add coverage for HPV types 31, 33, 45, 52, and 58, which are responsible for 20% of cervical cancers.⁸³ In the United States, because of cervical cancer screening and the rise in oropharyngeal HPV infections, the number of HPV-positive oropharyngeal squamous cell carcinomas is estimated to surpass the number of cervical cancers by the year 2020.⁸⁴ It is unknown whether prevention of the more common oncogenic HPV strains will lead to increased prevalence in other oncogenic HPV types, which may be even more oncogenic.

REFERENCES

1. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2014;63:1-30.
2. Centers for Disease Control and Prevention website. HPV vaccine information for clinicians - fact sheet. Available at: <http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-hcp.htm>. Accessed July 25, 2015.
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. *CA Cancer J Clin.* 2010;2010(60):277-300.
4. Centers for Disease Control and Prevention. Human papillomavirus-associated cancers - United States, 2004-2008. *MMWR Morb Mortal Wkly Rep.* 2012;61:258-261.

5. Centers for Disease Control and Prevention website. Cervical cancer statistics. Available at: <http://www.cdc.gov/cancer/cervical/statistics/index.htm>. Accessed July 25, 2015.
6. Wilson RM, Brown DR, Carmody DP, Fogarty S. HPV vaccination completion and compliance with recommended dosing intervals among female and male adolescents in an inner-city community health center. *J Community Health*. 2015;40:395-403.
7. Naud PS, Roteli-Martins CM, De Carvalho NS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. *Hum Vaccin Immunother*. 2014;10: 2147-2162.
8. Serrano B, Alemany L, Ruiz PA, et al. Potential impact of a 9-valent HPV vaccine in HPV-related cervical disease in 4 emerging countries (Brazil, Mexico, India and China). *Cancer Epidemiol*. 2014;38:748-756.
9. Joura EA, Ault KA, Bosch FX, et al. Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1997-2008.
10. Cifu AS, Davis AM. Use of HPV vaccine in males and females. *JAMA*. 2014;312:1920-1921.
11. American Cancer Society website. How much do the HPV vaccines cost? Are they covered by health insurance plans? Available at: <http://www.org/cancer/cancercauses/othercarcinogens/infectiousagents/hpv/humanpapillomavirusandhpvvaccinesfaq/hpv-faq-vaccine-cost>. Accessed July 25, 2015.
12. Schabert VF, Ye X, Insinga RP, Singhal PK, Riedel AA. Five-year routine cervical cancer screening rates and intervals in a US health plan. *Curr Med Res Opin*. 2008;24:2429-2435.
13. Ekwueme DU, Gardner JG, Subramanian S, et al. Cost analysis of the National Breast and Cervical Cancer Early Detection Program: selected states, 2003 to 2004. *Cancer*. 2008;112: 626-635.
14. Gamble HL, Klosky JL, Parra GR, Randolph ME. Factors influencing familial decision-making regarding human papillomavirus vaccination. *J Pediatr Psychol*. 2010;35:704-715.
15. Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus-related disease. *Am J Obstet Gynecol*. 2004;189:114-120.
16. Chesson HW, Ekwueme DU, Saraiya M, et al. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine*. 2012;30:6016-6019.
17. Bogaards JA, Kretzschmar M, Xiridou M, et al. Sex-specific immunization for sexually transmitted infections such as human papillomavirus: insights from mathematical models. *PLoS Med*. 2011;8:e1001147.
18. Kahn JA, Lan D, Kahn RS. Sociodemographic factors associated with high-risk human papillomavirus infection. *Obstet Gynecol*. 2007;110:87-95.
19. Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of male HPV vaccination in the United States. *Vaccine*. 2011;29:8443-8450.
20. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. *J Natl Cancer Inst*. 2008;100:308-320.
21. Diaz M, de Sanjose S, Ortendahl J, et al. Cost-effectiveness of human papillomavirus vaccination and screening in Spain. *Eur J Cancer*. 2010;46:2973-2985.
22. Lazenby GB, Unal ER, Andrews AL, Simpson K. A cost-effectiveness analysis of anal cancer screening in HIV-positive women. *J Low Genit Tract Dis*. 2012;16:275-280.
23. Dalla Pria A, Alfa-Wali M, Fox P, et al. High-resolution anoscopy screening of HIV-positive MSM: longitudinal results from a pilot study. *AIDS*. 2014;28:861-867.
24. Liszewski W, Ananth AT, Ploch LE, Rogers NE. Anal Pap smears and anal cancer: what dermatologists should know. *J Am Acad Dermatol*. 2014;71:985-992.
25. Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med*. 2000;108:634-641.
26. Goldie SJ, Kuntz KM, Weinstein MC, et al. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA*. 1999;281:1822-1829.
27. Kim JJ. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. *Lancet Infect Dis*. 2010;10:845-852.
28. Deshmukh AA, Chiao EY, Das P, Cantor SB. Clinical effectiveness and cost-effectiveness of quadrivalent human papillomavirus vaccination in HIV-negative men who have sex with men to prevent recurrent high-grade anal intraepithelial neoplasia. *Vaccine*. 2014;32:6941-6947.
29. Jit M, Brisson M, Laprise JF, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. *BMJ*. 2015;350:g7584.
30. European Medicines Agency website. Gardasil. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000703/human_med_000805.jsp&mid=WC0b01ac058001d124. Accessed July 25, 2015.
31. European Medicines Agency website. Cervarix. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000721/human_med_000694.jsp&mid=WC0b01ac058001d124. Accessed July 25, 2015.
32. Fierce Vaccines website. *Gardasil: new 2-dose schedule granted positive CHMP opinion for Europe's leading HPV vaccine*. Lyon, France: Fiercefavvines; 2014. Available at: <http://www.fiercefavvines.com/press-releases/gardasil-new-2-dose-schedule-granted-positive-chmp-opinion-europe-s-leading>. Accessed July 25, 2015.
33. US Department of Health and Human Services website. The Affordable Care Act and Immunization Department of Health and Human Services. Available at: <http://www.hhs.gov/opa/affordable-care-act/index.html>. Accessed July 25, 2015.
34. Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60: 1705-1708.
35. US Department of Health and Human Services website. Patient protection and Affordable Care Act of 2010. Available at: <http://www.hhs.gov/healthcare/rights/index.html>. Accessed July 25, 2015.
36. Glenn BA, Tsui J, Singhal R, et al. Factors associated with HPV awareness among mothers of low-income ethnic minority adolescent girls in Los Angeles. *Vaccine*. 2015;33:289-293.
37. World Health Organization website. Countries using HPV vaccine. Available at: http://www.who.int/immunization/diseases/hpv/decision_implementation/en/. Accessed July 25, 2015.
38. Bonanni P, Bechini A, Donato R, et al. Human papilloma virus vaccination: impact and recommendations across the world. *Ther Adv Vaccines*. 2015;3:3-12.
39. South African Government News Agency website. HPV vaccination campaign to be rolled out in schools. Available at: <http://www.sanews.gov.za/south-africa/hpv-vaccination-campaign-be-rolled-out-schools>. Accessed July 25, 2015.

40. Gavi the vaccine alliance website. GAVI funds vaccines to protect girls against cervical cancer. 2012. Available at: <http://www.gavi.org/library/news/press-releases/2013/gavi-funds-vaccines-to-protect-girls-against-cervical-cancer/>. Accessed July 25, 2015.
41. Australian Government website. HPV school vaccination program. Available at: <http://hpv.health.gov.au/>. Accessed July 25, 2015.
42. Immunize BC website. HPV (human papillomavirus) one-time vaccine program for young women. Available at: http://immunizebc.ca/sites/default/files/graphics/hpv_healthfile_imm_record_form_0.pdf. Accessed July 25, 2015.
43. Ontario Ministry of Health and Long-Term Care website. Ontario's HPV vaccination program. Available at: <http://www.health.gov.on.ca/en/ms/hpv/>. Accessed July 25, 2015.
44. Alberta Health Services website. Common questions about HPV. <http://immunizealberta.ca/i-need-know-more/common-questions/hpv>. Accessed July 25, 2015.
45. Public Health Agency of Canada website. Provincial and territorial immunization information. Available at: <http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/children-enfants/schedule-calendrier-eng.php>. Accessed July 25, 2015.
46. Austria Federal Ministry of Health. Available at: http://www.bmg.gv.at/home/Schwerpunkte/Gesundheitsfoerderung_Praevention/Impfen/HPV_Impfung. Accessed July 25, 2015.
47. European Cervical Cancer Association website. HPV vaccination across Europe. Available at: http://www.ecca.info/fileadmin/user_upload/HPV_Vaccination/ECCA HPV_Vaccination_April_2009.pdf. Accessed July 25, 2015.
48. Seme K, Maver PJ, Korac T, et al. Current status of human papillomavirus vaccination implementation in central and eastern Europe. *Acta Dermatovenerol Alp Pannonica Adriat*. 2013;22:21-25.
49. Judy S-I. HPV: to vaccinate or not to vaccinate. Israel News Jerusalem, Israel: The Jerusalem Post; 2013.
50. Centers for Disease Control and Prevention (CDC). Progress toward implementation of human papillomavirus vaccination—the Americas, 2006–2010. *MMWR Morb Mortal Wkly Rep*. 2011;60:1382-1384.
51. Larson HJ, Wilson R, Hanley S, Parys A, Paterson P. Tracking the global spread of vaccine sentiments: the global response to Japan's suspension of its HPV vaccine recommendation. *Hum Vaccin Immunother*. 2014;10:2543-2550.
52. Global Advisory Committee on Vaccine Safety, 11-12 December 2013. *Wkly Epidemiol Rec*. 2014;89:53-60.
53. Sutton I, Lahoria R, Tan I, Clouston P, Barnett M. CNS demyelination and quadrivalent HPV vaccination. *Mult Scler*. 2009;15:116-119.
54. Chang J, Campagnolo D, Vollmer TL, Bomprezzi R. Demyelinating disease and polyvalent human papilloma virus vaccination. *J Neurol Neurosurg Psychiatry*. 2011;82:1296-1298.
55. Wildemann B, Jarius S, Hartmann M, Regula JU, Hametner C. Acute disseminated encephalomyelitis following vaccination against human papilloma virus. *Neurology*. 2009;72:2132-2133.
56. Scheller NM, Svanstrom H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA*. 2015;313:54-61.
57. Centers for Disease Control and Prevention website. Frequently asked questions about HPV vaccine safety. Available at: http://www.cdc.gov/vaccinesafety/Vaccines/HPV/hpv_faqs.html. Accessed July 25, 2015.
58. Colafrancesco S, Perricone C, Tomljenovic L, Shoenfeld Y. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. *Am J Reprod Immunol*. 2013;70:309-316.
59. Khatun S, Akram Hussain SM, Chowdhury S, et al. Safety and immunogenicity profile of human papillomavirus-16/18 AS04 adjuvant cervical cancer vaccine: a randomized controlled trial in healthy adolescent girls of Bangladesh. *Jpn J Clin Oncol*. 2012;42:36-41.
60. Grimes RM, Benjamins LJ, Williams KL. Counseling about the HPV vaccine: desexualize, educate, and advocate. *J Pediatr Adolesc Gynecol*. 2013;26:243-248.
61. Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine. *Pediatr Infect Dis J*. 2010;29:95-101.
62. Centers for Disease Control and Prevention website. Summary of HPV adverse event reports published in JAMA. Available at: <https://web.archive.org/web/20150317013226/http://www.cdc.gov/vaccinesafety/Vaccines/HPV/jama.html>. Accessed July 25, 2015.
63. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*. 2009;302:750-757.
64. Demarteau N, Tang CH, Chen HC, Chen CJ, Van Kriekinge G. Cost-effectiveness analysis of the bivalent compared with the quadrivalent human papillomavirus vaccines in Taiwan. *Value Health*. 2012;15:622-631.
65. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374:301-314.
66. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356:1915-1927.
67. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356:1928-1943.
68. Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet*. 2006;367:1247-1255.
69. Munoz N, Kjaer SK, Sigurdsson K, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst*. 2010;102:325-339.
70. Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV) types 6, 11, 16, and 18 L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. *J Infect Dis*. 2009;199:926-935.
71. Wheeler CM, Castellsague X, Garland SM, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol*. 2012;13:100-110.
72. Szarewski A. HPV vaccine: Cervarix. *Expert Opin Biol Ther*. 2010;10:477-487.
73. Szarewski A. Cervarix(R): a bivalent vaccine against HPV types 16 and 18, with cross-protection against other high-risk HPV types. *Expert Rev Vaccines*. 2012;11:645-657.
74. Herrin D, Coates E, Costner P, et al. Comparison of adaptive and innate immune responses induced by licensed vaccines for human papillomavirus. *Hum Vaccin Immunother*. 2014;10:3446-3454.

75. Toft L, Tolstrup M, Muller M, et al. Comparison of the immunogenicity of Cervarix(R) and Gardasil(R) human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults. *Hum Vaccin Immunother.* 2014;10:1147-1154.
76. Harper DM, Vierthaler SL. Next generation cancer protection: the bivalent HPV vaccine for females. *ISRN Obstet Gynecol.* 2011;2011:457204.
77. Romanowski B. Long term protection against cervical infection with the human papillomavirus: review of currently available vaccines. *Hum Vaccin.* 2011;7:161-169.
78. Luna J, Plata M, Gonzalez M, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil in adult women. *PLoS One.* 2013;8:e83431.
79. Centers for Disease Control and Prevention website. HPV vaccine - questions & answers. August 6, 2014. Available at: <http://www.cdc.gov/vaccines/vpd-vac/hpv/vac-faqs.htm>. Accessed July 25, 2015.
80. Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. *Sex Health.* 2011;8:171-178.
81. Osborne SL, Tabrizi SN, Brotherton JM, et al. Assessing genital human papillomavirus genoprevalence in young Australian women following the introduction of a national vaccination program. *Vaccine.* 2015;33:201-208.
82. Garland SM, Brotherton JM, Condon JR, et al. Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program. *BMC Med.* 2011;9:104.
83. US Department of Health and Human Services, US Food and Drug Administration website. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm>. Accessed July 25, 2015.
84. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29: 4294-4301.

Answers to CME examination

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1. a
2. b

3. a

Cutaneous and mucocutaneous leishmaniasis

Clinical perspectives

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Learning objectives

After completing this learning activity participants should be able to recognize the cutaneous lesions in immigrants and travelers from endemic areas with leishmanial and delineate the modalities used in the diagnosis of the cutaneous lesions of leishmaniasis.

Disclosures

Editors

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Leishmaniasis is endemic in 98 countries and territories, with 1.2 million new cases per year, making it a worldwide concern. The deadly visceral form is a leading cause of death from tropical parasitic infections, second only to malaria. Leishmaniasis appears to be increasing in many countries because of extended urbanization. The disease reservoir includes small mammals; parasite transmission occurs via bite of the female phlebotomine sandfly. Disease manifestations vary and largely depend upon the *Leishmania* species acquired. It may be first evident with a range of findings—from a localized cutaneous ulcer to diffuse painless dermal nodules—or, in the mucocutaneous form, ulceration of the oropharynx. In the potentially deadly visceral form, the internal organs and bone marrow are affected. (J Am Acad Dermatol 2015;73:897-908.)

Key words: bat; dog; gerbil; kala-azar; leishmaniasis; parasitic disorders; protozoan diseases; rodents; sandfly; tropical diseases; ulcer.

INTRODUCTION

Leishmaniasis is a widespread parasitic disease that is seen predominantly in children and young adults, although it may occur at any age. Because of the enhanced opportunity for exposure and possibly not having a full developed immune system, children may be more susceptible to infection than adults.¹ Children are most vulnerable to being bitten by the sandfly, which transmits the *Leishmania* parasite,

Abbreviations used:

LRV: Leishmania RNA virus

PKDL: post-kala-azar dermal leishmaniasis

WHO: World Health Organization

while indoors asleep or while outdoors.²⁻⁴ This disorder can affect both visceral organs and cutaneous surfaces (Table 1). In its more common

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cutaneous form, it is characterized by ulcers on the face and extremities, which, even after healing, may disfigure a child and lead to social stigma.⁶⁻⁸ The World Health Organization (WHO) estimates that up to 1.2 million cases of cutaneous leishmaniasis occur each year in 98 countries and territories on 5 continents.⁹ In its visceral form, which affects up to 400,000 people worldwide each year, the mortality rate is 10%, making it the second most deadly tropical parasitic infection in the world after malaria.^{9,10} Unlike visceral leishmaniasis, which is concentrated in India, Bangladesh, South Sudan, Sudan, Brazil, and Ethiopia, cutaneous leishmaniasis is evenly distributed in Western Asia, the Mediterranean region, and Latin America.^{9,11} A recent rise in diagnoses in the United States has been noted and is attributable to international travel to and from endemic regions, whether by immigrants, refugees, tourists, or soldiers.^{9,12,13} Cutaneous leishmaniasis is endemic in southern Texas, and may also be so in northeastern Texas and southeastern Oklahoma, where a growing number of cases are being reported.¹³⁻¹⁶

HISTORY

Key points

- The organism was first observed by Cunningham in 1885
- In 1903, leishmaniasis, named for William Leishman, was described as causative agent of kala-azar
- In 1942, sandflies were proven to be the vector of leishmaniasis

Incan clay pottery depicting mutilations and other deformities suggests that American leishmaniasis may have been present during pre-Columbian times.¹⁷ The Leishmania organism was first observed by Cunningham¹⁸ in 1885 using tissue specimens from a “Delhi boil.”^{19,20} He concluded that the responsible organism was not bacterial, which was the popular belief at that time. Borovsky, a Russian military surgeon working in Tashkent in 1898, described the organism in further detail, observing that the parasite was a protozoan.^{19,21} His findings were independently confirmed by Wright in 1903.²⁰ In that same year, the causative agent of kala-azar was described by both William Leishman²² in London and Charles Donovan²³ in Chennai.²⁰ Although by 1928 induction of cutaneous leishmaniasis was observed in those bitten by sandflies of the genus *Phlebotomus*, it was not until 1942 when sandflies were decisively proven to be the vector for both cutaneous and visceral leishmaniasis.^{21,24,25} Only female phlebotomine sandflies have been found to be vectors. Vectorial

Table I. Types of leishmaniasis

Leishmaniasis syndromes	Presentation
Cutaneous	Onset within several weeks or months of exposure; typically progress from small papules to plaques and then to painless ulcers; regional lymphadenopathy and satellitosis may be evident
Mucocutaneous	In those infected in the Americas; may present years after cutaneous lesions have healed; presents as nasal congestion, bleeding, and mucosal erosions or inflammation; the mouth is less commonly affected than the nose; perforation of the nasal septum and destruction of the mouth, nose, and pharynx may occur
Visceral	Weeks to months after sandfly bite, those who become symptomatic may have fever, hepatosplenomegaly, weight loss, and pancytopenia; affects internal organs, typically the spleen, liver, and bone marrow

Data from Peters et al.⁵

competence of sandflies for different species of *Leishmania* is controlled by surface structural polymorphisms.²⁶

EPIDEMIOLOGY

Key points

- Leishmaniasis is endemic to all continents except Australia and Antarctica
- The worldwide prevalence of people infected with leishmaniasis is estimated at 12 million
- Its incidence in the United States is on the rise
- It appears to be becoming more common worldwide because of urbanization
- Ninety percent of new infections occur in Afghanistan, Iran, Saudi Arabia, Syria, Brazil, and Peru

Leishmaniasis is caused by protozoan parasites from more than 20 *Leishmania* species. This disease is endemic in every continent except Australia and Antarctica. Among the WHO’s list of “neglected” tropical infections, the estimated disease burden of leishmaniasis places it second in mortality and fourth in morbidity worldwide.^{10,27} The incidence of cutaneous leishmaniasis in the United States has

been increasing for several reasons; Americans traveling to endemic areas and immigrants from these regions account for much of this rise.^{3,28,29} In addition, the recent activity of US troops in the Middle East has added to cases of leishmaniasis encountered in the United States.³⁰ Between 2001 and 2006, there have been 1287 reported cases of US military personnel infected with leishmania during service in Iraq and Afghanistan.²⁸ There were another 522 reported cases between 2002 and 2004 in personnel who served in southwest and central Asia.²⁸ The manifestations of leishmaniasis are dependent upon the responsible species, which have geographic predilections. Old World leishmaniasis is endemic in Asia, Africa, the Mediterranean region, and the Middle East. The species responsible for Old World disease include *Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, and *Leishmania donovani*.^{11,31,32} The cutaneous lesions caused by *L tropica*, which is hosted by the hyrax, a small mammal, are known by several names, including Oriental sore, Baghdad boil, and Delhi boil.^{33,34} *L major* and *L aethiopica* cause cutaneous lesions as well, whereas *L donovani* is implicated in visceral leishmaniasis, also known as kala-azar or black fever. In the Middle East, sandflies are most active between the months of April and November.³⁵ In New World leishmaniasis, the offending parasites include *Leishmania mexicana*, *Leishmania braziliensis*, and *Leishmania guyanensis*. Its distribution range includes Central America, most of South America, and southern Texas.³⁶ *L mexicana*, hosted by various forest rodents in Central America and the Southern Plains wood rat (*Neotoma micropus*) in southern Texas, may cause lesions similar to the Old World ulcers, roughly 50% of the time on the ear, referred to as a chiclero's ulcer. It rarely disseminates into diffuse cutaneous leishmaniasis.^{6,37-40} In Texas, there is an increase in transmission in the fall.¹⁵ In addition to cutaneous lesions, *L braziliensis* complex, *Leishmania panamensis*, and *L guyanensis* can cause the mutilating destructive mucocutaneous leishmaniasis, referred to as espundia.⁴¹ *Leishmania peruviana*, which is part of the *L braziliensis* complex, causes cutaneous and mucocutaneous disease, known as uta, its vector residing 1000 to 3000 meters above sea level in the Peruvian Andes.⁴²

According to the 1990 report by the WHO, the estimated worldwide prevalence of leishmaniasis was 12 million.³¹ A 2010 WHO report proclaimed that there are 350 million people in endemic areas at risk of developing leishmaniasis in 98 countries and territories worldwide.^{11,43} As a result of underreporting by countries, it is impossible to precisely determine the change in incidence. A 2012 WHO report

estimated the annual incidence of cutaneous leishmaniasis is 1.1 to 1.6 million cases with 90% occurring in India, Bangladesh, Sudan, South Sudan, Brazil, and Ethiopia.⁹ The highest case counts are in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, Sudan, Costa Rica, and Peru.^{9,44,45} When considering disease in the New World alone, *L braziliensis* complex accounts for the most cases of human disease and has the widest geographic distribution in the Americas.³⁶ The incidence in the Americas is probably higher than the reported rate, and is approximated at 100,000 new cases annually.⁴⁴ There is concern in both of the Americas, East Africa, and Asia that new housing developments in areas where the parasite exists and increased contact between hosts and vectors as a result of environmental change, such as droughts, may cause an increase in leishmaniasis.^{13,46,47} Although the incidence appears to decline from 1990 estimates, the 2012 report cautions this to be a conservative estimate because of broad underreporting; many affected individuals do not have medical care access or have been misdiagnosed.⁴⁸

Sandflies favor resting and breeding in cooler climates with thick vegetation as opposed to urban settings.⁴⁶ Rapid urbanization and changes in precipitation have been linked to changes in leishmaniasis infection. Growth of metropolitan areas in Brazil has caused a reemergence of New World leishmaniasis.⁴⁹ Domestic dogs are the predominant reservoir of *Leishmania infantum*, but removing seropositive canines has not been an adequate method of reducing incidence of leishmaniasis, because up to 20% of canines are seropositive in Brazil.⁴⁹ In the past decade, eastern Jerusalem has seen a sharp increase in *L tropica* in both areas of poor and modern waste management. Incidence in Israel has also risen with the extension of residential neighborhoods into previously uninhabited areas.⁴⁶ Dry spells have created increases in the number of cases of New World leishmaniasis during drought in Texas and periods of decreased rainfall in Colombia.^{13,50}

ETIOLOGY

Key points

- The genus *Leishmania* is divided into 2 subgenera: *Leishmania* and *Viannia*
- Leishmaniasis is transmitted by female sandflies
- Sandflies are silent and tiny, being one-third the size of a mosquito
- Reservoirs include man, dogs, leopards, hyenas, rodents, bats, and baboons

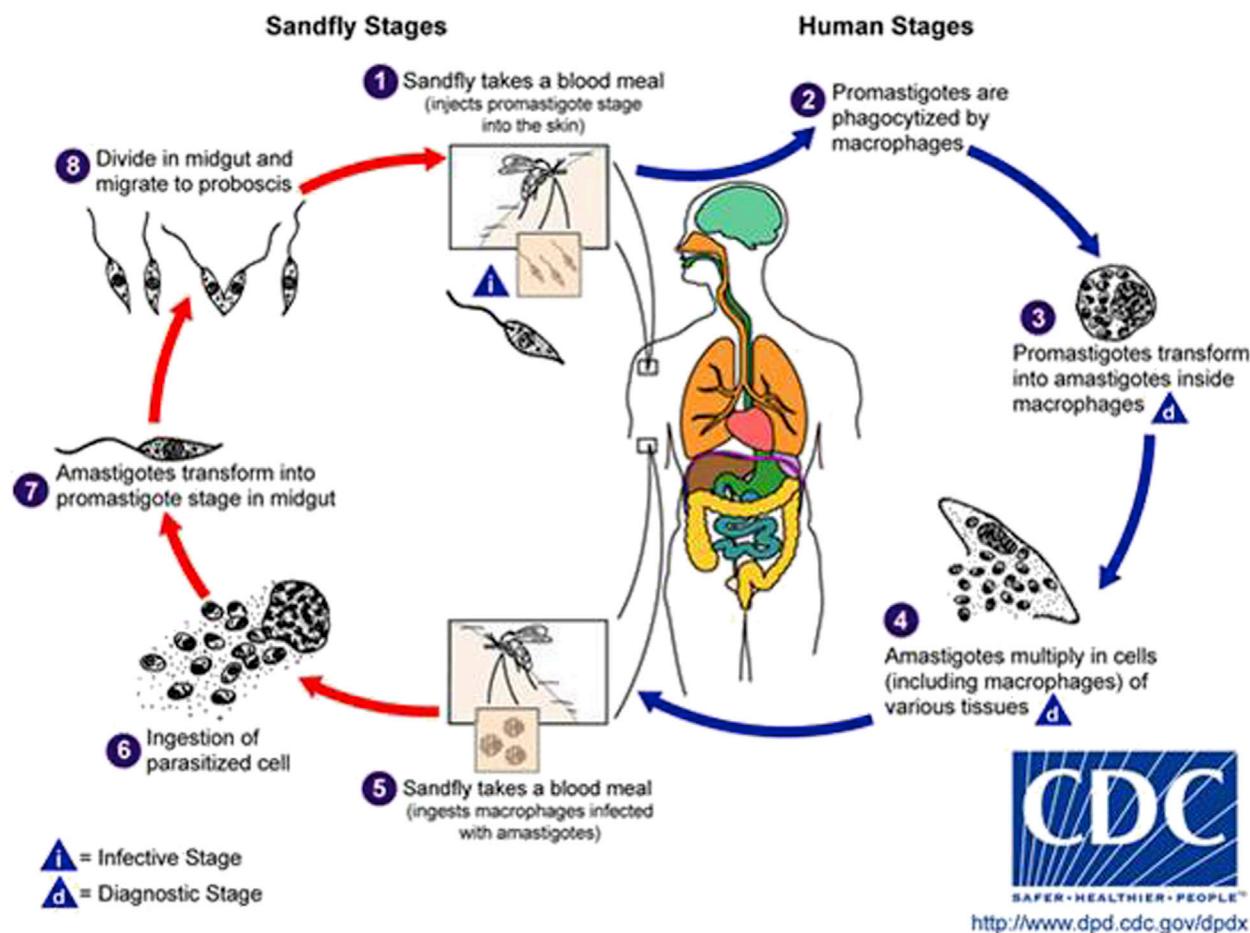


Fig 1. Leishmaniasis. Life cycle. Leishmaniasis is transmitted by the bite of infected female phlebotomine sandflies. (1) The sandflies inject the infective stage (ie, promastigotes) from their proboscis during blood meals. (2) Promastigotes that reach the puncture wound are phagocytized by macrophages and other types of mononuclear phagocytic cells. (3) Promastigotes transform in these cells into the tissue stage of the parasite (ie, amastigotes), which (4) multiply by simple division and proceed to infect other mononuclear phagocytic cells. Parasite, host, and other factors affect whether the infection becomes symptomatic and whether cutaneous or visceral leishmaniasis results. (5, 6) Sandflies become infected by ingesting infected cells during blood meals. In sandflies, amastigotes transform into promastigotes, (7) develop in the gut (in the hindgut for leishmanial organisms in the *Viannia* subgenus and in the midgut for organisms in the *Leishmania* subgenus), and (8) migrate to the proboscis. Courtesy of the Centers for Disease Control and Prevention.

Leishmaniasis is caused by parasites of the genus *Leishmania*. They are transmitted by female sandflies and have adapted to canines and man, as well as several other mammalian species, including rodents, bats, baboons, leopards, and hyenas.⁵¹ The life cycle of the unicellular *Leishmania* species begins in the gut of the phlebotomine sandfly, which belongs to the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World.^{36,52} The sandfly is a small insect that is silent and one-third the size of a mosquito. These insects rest during the day in cooler areas of vegetation and are active between dusk and dawn; bites may or may not be painful.⁵³ The sandfly

has a life span of about 30 days and is actually a poor flier, going up to only approximately 2 meters, covering only short distances at a time.²¹

Identification of an RNA virus, *Leishmania* RNA virus (LRV)-1 in New World parasites, *L brasiliensis* and *L guyanensis*, and LRV-2 in Old World parasite, *L major*, has led to the belief that development of mucocutaneous leishmaniasis is virally mediated.⁵⁴⁻⁵⁷ LRV is a member of the Totiviridae family and has a double-stranded RNA genome that encodes a RNA-dependent RNA polymerase in order to undergo viral double-stranded RNA replication and single-strand RNA transcription.⁵⁸ The virus may be recognized by

Table II. Clinical disease of leishmaniasis in humans

Leishmania species	Clinical features	Main reservoir host
New World		
<i>L mexicana</i>	Cutaneous	Forest rodents
<i>L braziliensis</i>	Cutaneous and mucocutaneous	Rain forest rodents
<i>L guyanensis</i>	Cutaneous	Two-toed forest sloth
<i>L amazonensis</i>	Cutaneous	Rain forest rodents, marsupial, and fox
<i>L panamensis</i>	Cutaneous and mucocutaneous	Tree sloth
<i>L venezuelensis</i>	Cutaneous	Unknown
<i>L lainsoni</i>	Cutaneous	Forest rodent
<i>L garnhami</i>	Cutaneous	Opossum
<i>L pifanoi</i>	Cutaneous	Unknown
<i>L peruviana</i>	Cutaneous	Dog
<i>L colombiensis</i>	Cutaneous	Sloth
Old World		
<i>L donovani</i>	Cutaneous and visceral	Dog, fox, opossum, and rat
<i>L tropica</i>	Cutaneous	Rock hyrax
<i>L major</i>	Cutaneous	Gerbils and other rodents
<i>L aethiopica</i>	Cutaneous	Hyrax
<i>L killicki</i>	Cutaneous	Unknown
Old and New World		
<i>L infantum</i>	Cutaneous and visceral	Dog

Data from Spickler, Galyon, and Lofstedt,³³ Matayoshi et al,⁶² and Suster and Ronnen.⁶³



Fig 2. Clustered nodules of leishmaniasis on cheek of a Yemeni patient.

the host Toll-like receptor 3, initiating destruction of the parasite, creating dispersal of LRV and triggering a metastatic hyperinflammatory reaction of proinflammatory cytokines and chemokines.⁵⁸

Parasite life cycle

Key points

- This parasite is extracellular and flagellated in its promastigote form
- It multiplies in the vector's gut by binary fusion
- The parasite enters its host when the female sandfly feeds
- The parasite becomes intracellular and non-flagellated in its host
- The cycle is completed when the sandfly feeds on an infected host

In these insect vectors, the parasites are flagellated and are found extracellularly. At this stage, the dimorphic organism is in its promastigote or leptomonad form, which multiplies in the vector's gut via binary fission.^{21,59} After migrating to the salivary glands, the parasites enter the host when the female sandfly feeds, which usually occurs on exposed areas of the body.⁶⁰ Once inside human, canine, or rodent hosts, the parasites are ingested by dermal macrophages, where they exist as intracellular non-flagellated organisms, beginning the other half of their life cycle as amastigotes or leishmanial forms^{21,59,61} (Fig 1). The cycle is completed when the sandfly feeds on an infected host, and the parasite moves to the gut where metamorphosis into the promastigote form takes place.

The etiology of the various disease expressions is caused by several different organisms of the genus *Leishmania* (Table II). This genus is divided into 2 subgenera, *Leishmania* and *Viannia*, the former consisting of leptomonads that multiply anterior to the pylorus in the gut of the sandfly and the latter comprised of leptomonads replicating in the mid- and hindgut.^{11,31} These are further classified into the complexes; *L donovani*, *L tropica*, *L major*, *L aethiopica*, and *L mexicana* form the subgenus *Leishmania*, and *L braziliensis* and *L guyanensis* form the subgenus *Viannia*.^{11,31,64} Finally, the complexes are composed of species based on intrinsic qualities of the parasite, such as isoenzymes. The taxonomic classification for *Leishmania* complexes

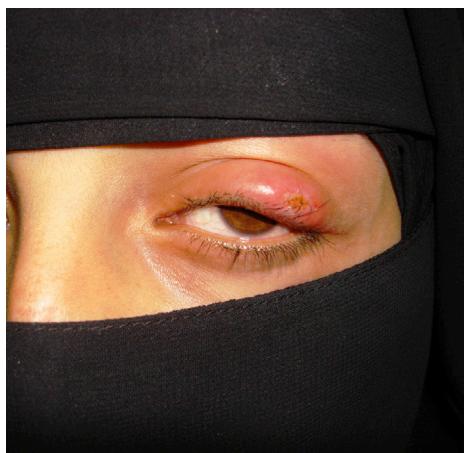


Fig 3. Ulcerated plaque on the eyelid caused by Old World leishmaniasis.



Fig 4. Multiple ulcers on the legs caused by Old World leishmaniasis.

and species are frequently being revised because of the discovery of new organisms with subtle variations of known species.⁶⁵

CLINICAL MANIFESTATIONS

Old World cutaneous leishmaniasis

Key points

- Old World cutaneous leishmaniasis may present in the following forms: localized, chronic relapsing, or diffuse



Fig 5. Erosion on a lip caused by Old World leishmaniasis.



Fig 6. Solitary ulcer from leishmaniasis in American tourist who traveled to Southern Africa and who also has African rickettsiosis.



Fig 7. Slowly progressing nodules on the face at the periphery of old scars from cutaneous ulceration, from chronic relapsing cutaneous leishmaniasis (leishmania recidivans).

- Acute cutaneous leishmaniasis often resembles a furuncle or *Staphylococcus aureus* infection
- Infection with *Leishmania tropica* typically causes <3 ulcers, the majority occurring on the head, and resolves within 2 years
- *Leishmania major* infections usually feature >3 ulcers that are self-limited and heal within 1 year

Old World cutaneous leishmaniasis has 3 different forms: localized, chronic relapsing, and diffuse.



Fig 8. Leishmaniasis. Multiple cutaneous crusted erosive plaques in tourist who returned from a rainforest in South America, caused by *Leishmania panamensis*.



Fig 9. Leishmaniasis. More exudative ulcers, 1 month later, in the same untreated patient who had returned from the South American rainforest.



Fig 10. Leishmaniasis. Well demarcated leg ulcers in an American medical student who returned from a tropical medicine elective in the rainforest of Ecuador, caused by *Leishmania braziliensis*.

Localized cutaneous leishmaniasis has an incubation period that typically ranges from 2 to 4 weeks, but that may range from a few days to 3 years.⁶⁶ It begins as an asymptomatic papule or papules, developing occasionally with nodules, at the site of the sandfly bite. The papules enlarge and form well circumscribed ulcers with a raised violaceous border caused by epidermal breakdown (Figs 2-6).⁶⁷ Acute



Fig 11. Colonoscopy in diffuse cutaneous leishmaniasis in a patient with AIDS from Central America.

cutaneous leishmaniasis often is mistaken for furuncles, furuncular myiasis, or *Staphylococcus aureus* infection.^{68,69} When a lesion heals, it forms a depressed scar. *L tropica* infection results in few lesions; 63% of affected individuals have 1 lesion and 95% have <3 lesions.⁷⁰ Sixty percent to 76% occur on the head or neck, with 30% to 36% noted on the extremities and the rest on the trunk.¹ The lesions are usually self-limited, with 73% spontaneously healing within 2 years.⁷⁰ In contrast to *L tropica*, *L major* typically results in multiple ulcers ranging in number from 1 to 20.⁷¹ However, it is also a self-limited disease, with healing usually occurring within a year.⁴ Cutaneous leishmaniasis caused by *L aethiopica* gives rise to slower-growing ulcers than the other Old World types. These will also take longer to heal—usually between 2 and 5 years.¹¹ *L aethiopica* is the organism responsible for diffuse cutaneous leishmaniasis in the Old World, which is rare. Chronic relapsing cutaneous leishmaniasis, or leishmania recidivans, is predominantly caused by *L tropica*. It manifests as slowly progressing papules, usually occurring on the face at the periphery of old scars, in patients with a previous cutaneous ulceration^{11,31} (Fig 7). In 1 study, the mean age of onset of lesions ranged from 10 months to 8 years.⁴

New World cutaneous leishmaniasis

Key points

- *Leishmania braziliensis* infection often causes severe disease
- A host may be infected by 2 Leishmania species simultaneously
- *Leishmania mexicana* may induce an ear ulceration, referred to as a chiclero's ulcer
- *Leishmania panamensis* infection may produce a nonhealing, spreading ulceration along lymphatic channels



Fig 12. Diffuse cutaneous leishmaniasis in a patient with AIDS from Central America.



Fig 13. Cutaneous nodules on hand in diffuse cutaneous leishmaniasis in a patient with AIDS from Central America.

New World cutaneous leishmaniasis also has several clinical forms (Figs 8-10). Chiclero's ulcer, caused by *L mexicana*, originally seen in gum (chicle) collectors, consists of a slowly evolving ulcer occurring on the face or pinna of the ear. It takes no more than 6 months to develop and may persist for 20 years.^{11,31} Uta is a form predominantly seen in preschool age children in Peru. It is caused by *L peruviana* and manifests as a few self-healing cutaneous lesions that involve the mucosa only by contiguous spread.⁶ Although rare, 2 different species of Leishmania may coinfect the same reservoir. For example, a patient in Peru with cutaneous leishmaniasis may have simultaneous infections of *L braziliensis* and *Leishmania lainsoni*.⁷² Simultaneous infection of *L tropica* and *Rickettsia typhi* and *Rickettsia rickettsii* may also occur.⁷³ *L panamensis* gives rise to "ulcera de Bejuco," which is characterized by shallow ulcers that frequently metastasize along lymphatic channels. These lesions do not heal spontaneously and may cause nasopharyngeal mucosal destruction in 2% to 5% of cases.⁶ *L braziliensis* infection results in severe cutaneous disease that is more frequently associated with satellite papules, subcutaneous nodules, and lymph node involvement than the other types of Leishmania.⁴ It usually requires treatment to eradicate. *L guyanensis* causes multiple ulcers that may



Fig 14. Leishmaniasis embedded in squamous cell carcinoma in the conjunctiva of a patient with HIV.

spread along the lymphatics, resembling sporotrichosis. This condition, known regionally as "pian-bois," requires treatment for cure and frequently recurs.^{11,31}

Diffuse cutaneous leishmaniasis

Key points

- **Diffuse cutaneous leishmaniasis is comprised of painless nodules that may affect most of the skin on the body**
- **Thirty percent of patients with diffuse cutaneous leishmaniasis will have oral or nasopharyngeal involvement**
- **The causative species are *Leishmania aethiopica* in the Old World and *Leishmania mexicana* in the New World**
- **Colonic infiltration has been observed in patients with immune reconstitution inflammatory syndrome**

Diffuse cutaneous leishmaniasis was first described in 1913 by Thomson and Balfour⁷⁴ in Africa. It appears as painless nodules that slowly progress and eventually affect nearly the entire cutaneous surface, although it has a predilection for the skin of the face, ears, elbows, and knees.⁷⁵ In some cases, the rash may have a xanthomatous or verrucous appearance.⁴⁵ Thirty percent of cases eventually develop parasitic invasion of the nasopharyngeal and oral mucosa.⁷⁶ The lesions contain an abundance of parasites and give the face and ears a characteristic leonine facies that mimics lepromatous leprosy.⁷⁷ Secondary infection of lesions is common.⁷⁷ The offending parasites are *Laethiopica* in the Old World form and *L mexicana* in the New World.³¹ Therapy is required regardless of etiology, but resistance to treatment is extremely common. An altered cellular immune response prevents an appropriate T_H2 type reaction, resulting in disease chronicity.⁷⁶ Diffuse cutaneous leishmaniasis with large hypopigmented skin lesions may mimic tuberculoid leprosy.⁷⁸ Diffuse cutaneous leishmaniasis, which may include colonic infiltration, has been described in the

setting of immune reconstitution inflammatory syndrome after the initiation of highly active retroviral therapy^{79,80} (Figs 11-13). Leishmaniasis should be regarded as an immune reconstitution inflammatory syndrome-linked disease.⁷⁹

Mucocutaneous leishmaniasis

Key points

- Mucocutaneous leishmaniasis usually occurs after resolution of cutaneous lesions
- Nasal and oral cavities are preferentially affected
- Mucocutaneous leishmaniasis rates range from 3% to 20% in endemic areas

Mucocutaneous leishmaniasis usually occurs after the apparent resolution of cutaneous infection,⁸¹ although it can coexist with skin involvement.⁸² Lesions normally appear within 2 years of cutaneous infection, but may take as many as 30 years.⁸² The route of infection spread may be either hematogenous or lymphatic.⁷⁷ *L braziliensis* accounts for most cases of mucocutaneous leishmaniasis, but *L panamensis*, *L guyanensis*, and *Leishmania amazonensis* have also been implicated.⁶⁰ The nasal and oral cavities are preferentially affected; ulcerative lesions may extend into the oropharynx and the trachea.⁷⁷ Cartilage and vocal cords are susceptible to the parasite; bony structures are spared.⁷⁷ Mucocutaneous disease can be markedly disfiguring and even life-threatening; treatment is essential to control the disease. In endemic countries, the percentage of cases of cutaneous leishmaniasis with subsequent mucosal involvement is about 3% to 5%, but may be as high as 20% or more in certain regions.⁸³ It is unknown why some are more susceptible to mucocutaneous leishmaniasis while others develop only the cutaneous form. Men may be more susceptible.^{11,83}

Visceral leishmaniasis

Key points

- Visceral leishmaniasis is also known as kala-azar
- Visceral leishmaniasis often affects the liver, spleen, and bone marrow
- Visceral leishmaniasis is caused by *Leishmania donovani*, *Leishmania infantum*, or *Leishmania chagasi*
- Cutaneous leishmaniasis in those with resolved visceral leishmaniasis is referred to as post-kala-azar dermal leishmaniasis

Visceral leishmaniasis, or kala-azar, affects the liver, spleen, bone marrow, and other viscera. An associated cutaneous disease may occur, referred to

as post-kala-azar dermal leishmaniasis (PKDL). The presentation is dependent upon the species causing the infection. In East Africa, approximately 2% of patients with visceral leishmaniasis develop PKDL. A papular rash appears on the face and upper extremities during, or several months after, treatment of visceral disease.⁸⁴ This form is not disfiguring and tends to resolve without any additional therapy. The epidemiologic and clinical manifestations are different in India, where Bramachari⁸⁵ first described the disease.⁸ In India, 20% of patients with visceral leishmaniasis develop cutaneous disease years after the visceral involvement resolves.⁸⁶ PKDL is first evident with depigmented, nonulcerating macules or plaques on the face, neck, trunk, and extremities, and is usually followed by nodules on similar areas of the body.^{84,86} Because of an overlapping geographic location and clinical appearance, PKDL is often confused with leprosy. PKDL rarely occurs in China and South America; to our knowledge, it has not been described in the Mediterranean area.^{84,86}

Visceral leishmaniasis is usually caused by the *L donovani* complex, which includes *L donovani*, *L infantum*, and *L chagasi*.⁸⁷ Visceral leishmaniasis has also been reported with infection from *L tropica*.⁸⁸ The *L donovani* complex may coexist with HIV infection where leishmaniasis is endemic or in HIV patients who have traveled to these areas.⁸⁹ Multiple patients with HIV have developed visceral leishmaniasis, including cases of Leishmania within Kaposi sarcoma lesions.⁹⁰⁻⁹² Leishmania may exist within cutaneous cancers, including both basal cell and squamous cell carcinomas^{62,63} (Fig 14). Because the parasite may be found in unaffected skin, its presence in a biopsy specimen may be simply an incidental finding.^{5,91,92}

REFERENCES

1. Solomon M, Schwartz E, Pavlotsky F, Sakka N, Barzilai A, Greenberger S. Leishmania tropica in children: a retrospective study. *J Am Acad Dermatol*. 2014;71:271-277.
2. Goldman L. Types of American cutaneous leishmaniasis—dermatological aspects: a review. *Am J Trop Med Hyg*. 1947; 27:561-584.
3. Kim YA, Schwartz RA. *The influence of migration and travel. United States of America Global Dermatology Diagnosis and management according to geography, climate, and culture*. Berlin, Germany: Springer-Verlag; 1994. pp. 45-50.
4. Melby PC, Kreutzer RD, McMahon-Pratt D, Gam AA, Neva FA. Cutaneous leishmaniasis: review of 59 cases seen at the National Institutes of Health. *Clin Infect Dis*. 1992;15:924-937.
5. Peters BS, Fish D, Golden R, Evans DA, Bryceson AD, Pinching AJ. Visceral leishmaniasis in HIV infection and AIDS: clinical features and response to therapy. *Q J Med*. 1990;77:1101-1111.
6. Koff AB, Rosen T. Treatment of cutaneous leishmaniasis. *J Am Acad Dermatol*. 1994;31:693-708.

7. Rau RC, Dubin HV, Taylor WB. Leishmania tropica infections in travellers. *Arch Dermatol.* 1976;112:197-201.
8. Ross AJ, Schneider JS, Schwartz RA. An unusual granuloma in an American returning from India: clinically resembling cutaneous leishmaniasis. *Ariz Med.* 1982;39:376-377.
9. Alvar J, Velez ID, Bern C, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One.* 2012;7:e35671.
10. Mathers CD, Ezzati M, Lopez AD. Measuring the burden of neglected tropical diseases: the global burden of disease framework. *PLoS Negl Trop Dis.* 2007;1:e114.
11. World Health Organization. Control of the leishmaniases. *World Health Organ Tech Rep Ser.* 2010;949:1-186.
12. Bailey MS, Green AD, Ellis CJ, et al. Clinical guidelines for the management of cutaneous leishmaniasis in British military personnel. *J R Army Med Corps.* 2005;151:73-80.
13. Clarke CF, Bradley KK, Wright JH, Glowicz J. Case report: emergence of autochthonous cutaneous leishmaniasis in northeastern Texas and southeastern Oklahoma. *Am J Trop Med Hyg.* 2013;88:157-161.
14. Furner BB. Cutaneous leishmaniasis in Texas: report of a case and review of the literature. *J Am Acad Dermatol.* 1990;23:368-371.
15. Kerr SF, McHugh CP, Dronen NO Jr. Leishmaniasis in Texas: prevalence and seasonal transmission of *Leishmania mexicana* in *Neotoma micropus*. *Am J Trop Med Hyg.* 1995;53:73-77.
16. Wright NA, Davis LE, Aftergut KS, Parrish CA, Cockerell CJ. Cutaneous leishmaniasis in Texas: a northern spread of endemic areas. *J Am Acad Dermatol.* 2008;58:650-652.
17. Goldman L. Pre-Columbian leishmaniasis. *Arch Dermatol.* 1983;119:540.
18. Cunningham DD. On the presence of peculiar parasitic organisms in the tissue of specimens of Delhi Boil. *Sci Mem Med Offrs Army India.* 1885;1:21.
19. Farah FS, Malak JA. Cutaneous leishmaniasis. *Arch Dermatol.* 1971;103:467-474.
20. Hart DT. Cutaneous and visceral leishmaniasis: a historical perspective. *Trans R Soc Trop Med Hyg.* 1985;79:740-741.
21. Moschella SL. Diseases of the mononuclear phagocytic system. In: Moschella SL, ed. *Dermatology*. Philadelphia, PA: W.B. Saunders Company; 1985:972-983.
22. Leishman WB. On the possibility of the occurrence of trypanosomiasis in India. *Br Med J.* 1903;1:1252-1254.
23. Donovan C. On the possibility of the occurrence of trypanosomiasis in India. *Br Med J.* 1903;1:79.
24. Swaminath CS, Shortt BH, Anderson LA. Transmission of Indian kala-azar to man by the bites of phlebotomus argentipes. *Ind Jour Med Res.* 1942;30:473-477.
25. Wenyon CM. Kala-azar and Oriental sore: the problem of transmission. *Br Med J.* 1928;2:558-562.
26. Pimenta PF, Saraiva EM, Rowton E, et al. Evidence that the vectorial competence of phlebotomine sand flies for different species of Leishmania is controlled by structural polymorphisms in the surface lipophosphoglycan. *Proc Natl Acad Sci U S A.* 1994;91:9155-9159.
27. Bern C, Maguire JH, Alvar J. Complexities of assessing the disease burden attributable to leishmaniasis. *PLoS Negl Trop Dis.* 2008;2:e313.
28. Pavli A, Maltezou HC. Leishmaniasis, an emerging infection in travelers. *Int J Infect Dis.* 2010;14:e1032-e1039.
29. Demers E, Forrest DM, Weichert GE. Cutaneous leishmaniasis in a returning traveller. *CMAJ.* 2013;185:681-683.
30. Norton SA, Frankenburg S, Klaus SN. Cutaneous leishmaniasis acquired during military service in the Middle East. *Arch Dermatol.* 1992;128:83-87.
31. Control of the leishmaniases. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* 1990;793:1-158.
32. Ashford RW, Kohestany KA, Karimzad MA. Cutaneous leishmaniasis in Kabul: observations on a 'prolonged epidemic.' *Ann Trop Med Parasitol.* 1992;86:361-371.
33. Spickler AR, Roth JA, Galyon J, Lofstedt J. Charts. In: Spickler AR, ed. *Emerging and Exotic Diseases of Animals*. Ames, Iowa: Iowa State University; 2010:205-209.
34. Ajaoud M, Es-sette N, Hamdi S, El-Idrissi AL, Riyad M, Lemrani M. Detection and molecular typing of *Leishmania tropica* from *Phlebotomus sergenti* and lesions of cutaneous leishmaniasis in an emerging focus of Morocco. *Parasit Vectors.* 2013;6:217.
35. Katzenellenbogen I. Vaccination against oriental sore: report of results of five hundred and fifty-five inoculations. *Arch Derm Syphilol.* 1944;50:239-242.
36. Grimaldi G Jr, Tesh RB, McMahon-Pratt D. A review of the geographic distribution and epidemiology of leishmaniasis in the New World. *Am J Trop Med Hyg.* 1989;41:687-725.
37. Convit J, Kerdel-Vegas F. Disseminated cutaneous leishmaniasis: inoculation to laboratory animals, electron microscopy and fluorescent antibodies studies. *Arch Dermatol.* 1965;91:439-447.
38. Lainson R, Strangways-Dixon J. The epidemiology of dermal leishmaniasis in British Honduras: II. Reservoir-hosts of *Leishmania mexicana* among the forest rodents. *Trans R Soc Trop Med Hyg.* 1964;58:136-153.
39. Magill AJ. Leishmaniasis. In: Magill AJ, Ryan ET, Hill D, Solomon T, eds. *Hunter's Tropical Medicine and Emerging Infectious Diseases*. Philadelphia, PA: Elsevier; 2013:740-758.
40. Farrell JP, ed. *Leishmania*. Boston, MA: Kluwer Academic Publishers; 2002:1-193 Black SJ, Seed JR, eds. *World Class Parasites*; vol. 4. Boston, MA: Kluwer Academic Publishers; 2002:1-193.
41. Marsden PD. Mucosal leishmaniasis ("espundia" Escomel, 1911). *Trans R Soc Trop Med Hyg.* 1986;80:859-876.
42. Davies CR, Llanos-Cuentas EA, Sharp SJ, et al. Cutaneous leishmaniasis in the Peruvian Andes: factors associated with variability in clinical symptoms, response to treatment, and parasite isolation rate. *Clin Infect Dis.* 1997;25:302-310.
43. McGwire BS, Satoskar AR. Leishmaniasis: clinical syndromes and treatment. *QJM.* 2014;107:7-14.
44. Leishmaniasis in the Americas. *Epidemiol Bull.* 1994;15:8-13.
45. Kedzierski L. Leishmaniasis. *Hum Vaccin.* 2011;7:1204-1214.
46. Muller GC, Kravchenko VD, Rybalov L, Beier JC, Schlein Y. Characteristics of resting habitats of adult *Phlebotomus papatasii* in Neot Hakikar, an oasis south of the Dead Sea. *J Vector Ecol.* 2011;36(suppl 1):S179-S186.
47. Bekele S, Bekele Y, Mulatu F, et al. Recent trends of cutaneous leishmaniasis in Alert Hospital, Addis Ababa. *Ethiop Med J.* 2014;1(suppl):37-41.
48. Stockdale L, Newton R. A review of preventative methods against human leishmaniasis infection. *PLoS Negl Trop Dis.* 2013;7:e2278.
49. Esch KJ, Pontes NN, Arruda P, et al. Preventing zoonotic canine leishmaniasis in northeastern Brazil: pet attachment and adoption of community Leishmania prevention. *Am J Trop Med Hyg.* 2012;87:822-831.
50. Cardenas R, Sandoval CM, Rodriguez-Morales AJ, Franco-Paredes C. Impact of climate variability in the occurrence of leishmaniasis in northeastern Colombia. *Am J Trop Med Hyg.* 2006;75:273-277.

51. Sang DK, Njeru WK, Ashford RW. A possible animal reservoir for *Leishmania tropica* s.l. in Kenya. *Ann Trop Med Parasitol.* 1992;86:311-312.
52. Mustafa MB, Hussein SM, Ibrahim EA, al-Seghayer SM, al-Amri SA, Gradoni L. *Phlebotomus papatasii* (Scopoli), vector of zoonotic cutaneous leishmaniasis in Riyadh province, Saudi Arabia. *Trans R Soc Trop Med Hyg.* 1994;88:40.
53. Centers for Disease Control and Prevention website. Parasites — leishmaniasis. Leishmaniasis FAQs. Available at: http://www.cdc.gov/parasites/leishmaniasis/gen_info/faqs.html. Accessed October 18, 2014.
54. Tarr PI, Aline RF Jr, Smiley BL, Scholler J, Keithly J, Stuart K. LR1: a candidate RNA virus of Leishmania. *Proc Natl Acad Sci U S A.* 1988;85:9572-9575.
55. Hartley MA, Ronet C, Zangerer H, Beverley SM, Fasel N. Leishmania RNA virus: when the host pays the toll. *Front Cell Infect Microbiol.* 2012;2:1-15.
56. Ives A, Ronet C, Prevel F, et al. Leishmania RNA virus controls the severity of mucocutaneous leishmaniasis. *Science.* 2011; 331:775-778.
57. Scheffter SM, Ro YT, Chung IK, Patterson JL. The complete sequence of Leishmania RNA virus LRV2-1, a virus of an Old World parasite strain. *Virology.* 1995;212:84-90.
58. Zangerer H, Ronet C, Desponds C, et al. Detection of Leishmania RNA virus in Leishmania parasites. *PLoS Negl Trop Dis.* 2013;7:e2006.
59. Barsky S, Storino W, Salgea K, Knapp P. Cutaneous leishmaniasis: surgical management of a case with unusual clinical and histological features. *Arch Dermatol.* 1978;114:1354-1355.
60. Strazzulla A, Cocuzza S, Pinzone MR, et al. Mucosal leishmaniasis: an underestimated presentation of a neglected disease. *Biomed Res Int.* 2013;2013:805108.
61. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis.* 2007;7: 581-596.
62. Matayoshi S, Baddina-Caramelli C, Goldbaum M, Takei LM, Honda M, Kara-Jose N. Epidermoid carcinoma arising in an ocular Leishmania lesion. *Br J Ophthalmol.* 2000;84: 1331-1332.
63. Suster S, Ronnen M. Basal cell carcinoma arising in a leishmania scar. *Int J Dermatol.* 1988;27:175-176.
64. Mebrahtu YB, Van Eys G, Guizani I, et al. Human cutaneous leishmaniasis caused by *Leishmania donovani* s.l. in Kenya. *Trans R Soc Trop Med Hyg.* 1993;87:598-601.
65. de Paiva Cavalcanti M, Dantas-Torres F, da Cunha Goncalves de Albuquerque S, et al. Quantitative real time PCR assays for the detection of *Leishmania (Viannia) braziliensis* in animals and humans. *Mol Cell Probes.* 2013;27:122-128.
66. Goto H, Lindoso JA. Current diagnosis and treatment of cutaneous and mucocutaneous leishmaniasis. *Expert Rev Anti Infect Ther.* 2010;8:419-433.
67. Darmstadt GL, Lane AT, Tunnessen WW Jr. Picture of the month. Cutaneous leishmaniasis. *Am J Dis Child.* 1993;147: 1339-1340.
68. David CV, Craft N. Cutaneous and mucocutaneous leishmaniasis. *Dermatol Ther.* 2009;22:491-502.
69. Jacobs B, Brown DL. Cutaneous furuncular myiasis: human infestation by the botfly. *Can J Plast Surg.* 2006;14:31-32.
70. Sang DK, Njeru WK, Ashford RW. A zoonotic focus of cutaneous leishmaniasis due to *Leishmania tropica* at Utut, Rift Valley Province, Kenya. *Trans R Soc Trop Med Hyg.* 1994; 88:35-37.
71. Samady JA, Schwartz RA. Old World cutaneous leishmaniasis. *Int J Dermatol.* 1997;36:161-166.
72. Veland N, Valencia BM, Alba M, et al. Simultaneous infection with *Leishmania (Viannia) braziliensis* and *L. (V.) lainsoni* in a Peruvian patient with cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2013;88:774-777.
73. Schwartz RA, Kapila R, McElligott SC, Atkin SH, Lambert WC. Cutaneous leishmaniasis and rickettsial African tick-bite fever: a combination of exotic traveler's diseases in the same patient. *Int J Dermatol.* 2012;51:960-963.
74. Simpson MH, Mullins JF, Stone OJ. Disseminated anergic cutaneous leishmaniasis. An autochthonous case in Texas and the Mexican states of Tamaulipas and Nuevo Leon. *Arch Dermatol.* 1968;97:301-303.
75. Convit J, Reyes O, Kerdel F. Disseminated anergic American leishmaniasis; report of three cases of a type clinically resembling lepromatous leprosy. *AMA Arch Derm.* 1957;76: 213-217.
76. Ordaz-Farias A, Munoz-Garza FZ, Sevilla-Gonzalez FK, et al. Case report: transient success using prolonged treatment with miltefosine for a patient with diffuse cutaneous leishmaniasis infected with *Leishmania mexicana*. *Am J Trop Med Hyg.* 2013;88:153-156.
77. Goiham-Yahr M. American mucocutaneous leishmaniasis. *Dermatol Clin.* 1994;12:703-712.
78. Dassoni F, Abebe Z, Naafs B, Morrone A. Cutaneous and mucocutaneous leishmaniasis resembling borderline-tuberculoid leprosy: a new clinical presentation? *Acta Derm Venereol.* 2013;93:74-77.
79. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *Int J Dermatol.* 2008; 47:1263-1270.
80. Khalil EA, Khidir SA, Musa AM, et al. Post-kala-azar dermal leishmaniasis: a paradigm of paradoxical immune reconstitution syndrome in non-HIV/AIDS patients. *J Trop Med.* 2013; 1:1-7.
81. Daneshbod Y, Oryan A, Davarmanesh M, et al. Clinical, histopathologic, and cytologic diagnosis of mucosal leishmaniasis and literature review. *Arch Pathol Lab Med.* 2011; 135:478-482.
82. Samady JA, Janniger CK, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis. *Cutis.* 1996;57:13-20.
83. David C, Dimier-David L, Vargas F, Torrez M, Dedet JP. Fifteen years of cutaneous and mucocutaneous leishmaniasis in Bolivia: a retrospective study. *Trans R Soc Trop Med Hyg.* 1993; 87:7-9.
84. Rashid JR, Chunge CN, Oster CN, Wasunna KM, Muigai R, Gachihi GS. Post-kala-azar dermal leishmaniasis occurring long after cure of visceral leishmaniasis in Kenya. *East Afr Med J.* 1986;63:365-371.
85. Brahmachari UN. Sporadic kala-azar in Calcutta, with notes of a case treated with atoxyl. *Br Med J.* 1908;1:1286-1288.
86. Kumar PV, Sadeghi E, Torabi S. Kala azar with disseminated dermal leishmaniasis. *Am J Trop Med Hyg.* 1989;40:150-153.
87. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol.* 2002;9:951-958.
88. Kreutzer RD, Grogl M, Neva FA, Fryauff DJ, Magill AJ, Aleman-Munoz MM. Identification and genetic comparison of leishmanial parasites causing viscerotropic and cutaneous disease in soldiers returning from Operation Desert Storm. *Am J Trop Med Hyg.* 1993;49:357-363.
89. Niamba P, Goumbri-Lombo O, Traore A, Barro-Traore F, Soudre RT. Diffuse cutaneous leishmaniasis in an HIV-positive patient in western Africa. *Australas J Dermatol.* 2007;48:32-34.

90. Gallego MA, Aguilar A, Plaza S, et al. Kaposi's sarcoma with an intense parasitization by Leishmania. *Cutis*. 1996;57:103-105.
91. Yebra M, Segovia J, Manzano L, Vargas JA, Bernaldo de Quiros L, Alvar J. Disseminated-to-skin kala-azar and the acquired immunodeficiency syndrome. *Ann Intern Med*. 1988; 108:490-491.
92. Smith D, Gazzard B, Lindley RP, et al. Visceral leishmaniasis (kala azar) in a patient with AIDS. *Aids*. 1989;3:41-43.

Cutaneous and mucocutaneous leishmaniasis

Differential diagnosis, diagnosis, histopathology, and management

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Learning objectives

After completing this learning activity, participants should be able to describe the complexities in the management of cutaneous lesions of leishmaniasis and identify appropriate treatment plans for patients with cutaneous leishmaniasis.

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The diagnosis of leishmaniasis can be challenging because it mimics both infectious and malignant conditions. A misdiagnosis may lead to an unfavorable outcome. Using culture, histologic, and/or polymerase chain reaction study results, a diagnosis of leishmaniasis can be established and treatment initiated. Appropriate management requires an accurate diagnosis, which often includes identification of the specific etiologic species. Different endemic areas have varying sensitivities to the same medication, even within individual species. Species identification may be of practical value, because infections with select species have a substantial risk of visceral involvement. In addition, HIV and otherwise immunocompromised patients with leishmaniasis have a propensity for diffuse cutaneous leishmaniasis. For most New World Leishmania species, parenteral antimonial drugs remain the first line of therapy, while Old World species are easily treated with physical modalities. Historically, live organism vaccination has been used and is effective in preventing leishmaniasis, but results in an inoculation scar and an incubation period that may last for years. A more effective method of vaccination would be welcome. (J Am Acad Dermatol 2015;73:911-26.)

Key words: antimony; carbon dioxide slush; CDC; HIV; Leishmaniasis; ketoconazole; miltefosine; protozoa; sodium stibogluconate; tropical disease; vaccination; vaccine.

DIFFERENTIAL DIAGNOSIS

Key points

- **Leishmaniasis may mimic other infectious diseases and a variety of malignancies**
- **A second or third infection may coexist with cutaneous leishmaniasis**

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Leishmaniasis has many clinical manifestations and may appear similar to a wide variety of other conditions¹⁻³ (Table I; Fig 1). Differentiation between conditions that mimic cutaneous leishmaniasis may require microbiologic, cytologic, and/or histologic evaluation.⁴ These include disorders that

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Abbreviations used:

CDC:	Centers for Disease Control and Prevention
HLA:	human leukocyte antigen
NADPH:	nicotinamide adenine dinucleotide phosphate
PCR:	polymerase chain reaction
RFHT:	radiofrequency-induced heat therapy
RPMI:	Roswell Park Memorial Institute (medium)

are infectious, malignant, or other disorders such as pyoderma gangrenosum.⁵

In patients with a travel history to regions where leishmaniasis is endemic, leishmaniasis must be considered in the differential diagnosis of those having nonspecific systemic symptoms, such as fever, or examination findings, such as splenomegaly. A major obstacle to diagnosis is unfamiliarity with leishmaniasis. In 48% of American cases, it was the patient or patient's family who first considered the possibility of leishmaniasis.⁶ Patients with a history of malignancy that may clinically appear similar to cutaneous or visceral leishmaniasis should have the diagnosis of cutaneous or visceral leishmaniasis entertained (Table II). A delay in diagnosis, especially in visceral leishmaniasis, may prove fatal. In addition, leishmaniasis in immunosuppressed patients, such as those with leukemia or AIDS, may be aggressive, with visceral leishmaniasis refractory to treatment.⁷ Because of chronic inflammation from a *Leishmania* infection, a primary skin cancer may develop at the site of an old leishmanial scar.⁷ Chronic relapsing cutaneous leishmaniasis may also clinically resemble lupus vulgaris, a type of cutaneous tuberculosis, and tuberculoid leprosy.^{8,9} Cancer patients may not have an immune system that is able to produce a fever or splenomegaly, and therefore a clinical suspicion for leishmaniasis should be maintained in appropriate settings.⁷ In addition, those with immunodeficiencies may develop cryptic forms of infection with *Leishmania*. *Leishmania infantum* has been found in bone marrow aspirates in 11% of patients with HIV in the Mediterranean basin.¹⁰ The initiation of antiretroviral therapy has been shown to decrease the prevalence of clinical signs of visceral leishmaniasis in those with HIV.¹¹

Diffuse cutaneous leishmaniasis can be clinically indistinguishable from other infectious diseases¹² (Table III). Diffuse cutaneous leishmaniasis may mimic post-kala-azar dermal leishmaniasis (PKDL), but only the latter condition will have visceral disease.

When diagnosing cutaneous leishmaniasis, dual and triple infections should also be considered. Diffuse cutaneous leishmaniasis may mask another disease, such as leprosy or HIV disease.¹³

Table I. Differential diagnosis of cutaneous leishmaniasis

Infectious
Ecthyma
Furuncle
Carbuncle
Sporotrichosis
North American blastomycosis
Paracoccidiomycosis
Tuberculosis cutis
Syphilitic gumma
Yaws
Prototheca infection
Condyloma acuminata
Lupus vulgaris (similar to leishmania recidivans)
Tuberculoid leprosy
Cutaneous furuncular myiasis
Tungiasis
Neoplastic
Basal cell carcinoma
Squamous cell carcinoma
Lymphoma
Other
Insect bite
Xanthoma tuberosum
Sarcoidosis
Pyoderma gangrenosum



Fig 1. Lupoid plaque of the nose in a woman with Old World leishmaniasis.

Mucocutaneous leishmaniasis causes destructive changes suggestive of syphilis, yaws, rhinoscleroma, and oral squamous cell carcinoma⁴ (Table IV). Unlike syphilis and yaws, mucocutaneous leishmaniasis does not cause destruction of cartilage and, unlike rhinoscleroma, does not produce nasal septum perforation.^{4,14}

DIAGNOSIS

Key points

- World travel has brought leishmaniasis to nonendemic regions
- The US Centers for Disease Control and Prevention accepts submissions for leishmaniasis testing worldwide

Table II. Malignancies that may mimic cutaneous or visceral leishmaniasis

Basal cell carcinoma
Squamous cell carcinoma
Keratoacanthoma
Merkel cell carcinoma
Kaposi sarcoma
Lymphoma

Table III. Differential diagnosis of diffuse cutaneous leishmaniasis

Lepromatous leprosy
Lobomycosis
Lupus vulgaris

Table IV. Differential diagnosis of mucocutaneous leishmaniasis

Syphilis
Yaws
Rhinoscleroma
Oral squamous cell carcinoma
Sarcoidosis

- Diagnosis may also be made via polymerase chain reaction studies, serologic assays, isoenzyme analysis, monoclonal antibody analysis RPMI media, and NNN media

An increase in international travel has brought leishmaniasis to nonendemic regions, where it often creates diagnostic dilemmas. A detailed history, including that of travel in endemic areas or a sandfly bite, should be obtained.¹⁵ The sandfly bite may or may not be painful, so patients may not recall the inoculation. The clinical findings of leishmaniasis are usually distinct enough to suggest the diagnosis in endemic areas; papules, plaques, ulcers, or nodules may exist, depending on the type of leishmaniasis and stage of disease.

Dermatoscopic evaluation may be helpful in distinguishing cutaneous leishmaniasis from other clinically similar lesions. Two studies conducted on the Mediterranean coast—1 in Spain and another in Turkey—evaluated patients with histopathology-proven cutaneous leishmaniasis. Each had a lesion evaluated under dermatoscopy and, in addition to erythema and vascular structures seen in virtually all lesions, yellow, tear-like structures corresponding with keratin plugs were seen in 40% to 53% of the lesions, and a white, starburst-like pattern corresponding to parakeratotic hyperkeratosis in 19% to 39%.^{16,17}

The treatment for leishmaniasis is often prolonged and toxic; therefore, confirmation of the clinical diagnosis is desirable. Unfortunately, the parasite can only be identified in 70% of cases of cutaneous leishmaniasis and 50% of cases of mucocutaneous leishmaniasis, even in experienced hands.^{18,19} In order to assist in the diagnosis of leishmaniasis, the US Centers for Disease Control and Prevention (CDC) offers Roswell Park Memorial Institute (RPMI) medium to all practitioners in the United States, with only US federal clinics paying a fee. The CDC also provides no-charge evaluation of biopsy specimens, smear and dermal scrapings, and polymerase chain reaction (PCR) study analysis worldwide. At present, fees are only charged to submitting US government agencies (see information at: http://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis.pdf).^{20,21} The CDC recommends using several techniques and obtaining multiple specimens from different lesions—or different portions of the same lesion—in order to increase detection sensitivity.²⁰ The CDC also advises obtaining a sterile punch biopsy specimen of the ulcer's border, including affected and unaffected tissue, and trisecting the tissue. The first portion should be sent for histologic examination, the second rolled on a glass slide, then fixed with methanol and stained with Giemsa stain.²⁰ The final portion should be sent to the CDC for culture on provided RPMI media. At the CDC, it will be divided into 2 portions, 1 for culture on Novy-MacNeal-Nicolle (NNN) media, supplemented with RPMI, and the other portion used for PCR analysis.

HISTOPATHOLOGY

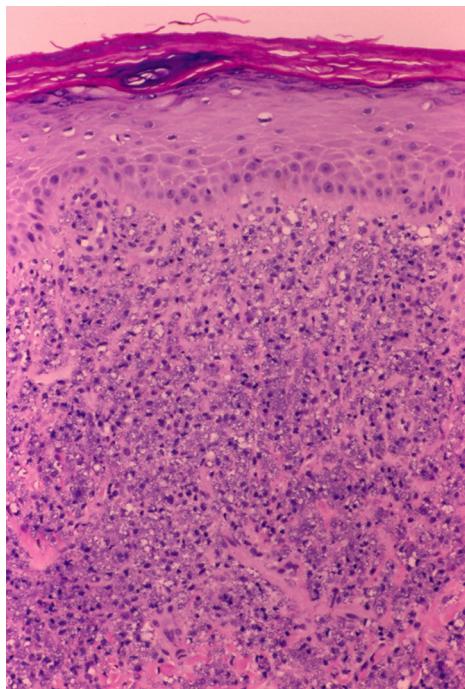
Key points

- Cutaneous leishmaniasis may feature amastigotes, a polycellular infiltrate, and/or granuloma formation
- Mucocutaneous leishmaniasis has 4 stages on histopathology: edematous, granulomatous, proliferative, and granulomatous necrotizing
- Chronic ulcers have fewer amastigotes compared to newer ones
- Diagnostic sensitivity is only about 60% in cases of Old World cutaneous leishmaniasis
- Amastigotes, known as Leishman–Donovan bodies, may sometimes be evident within macrophages

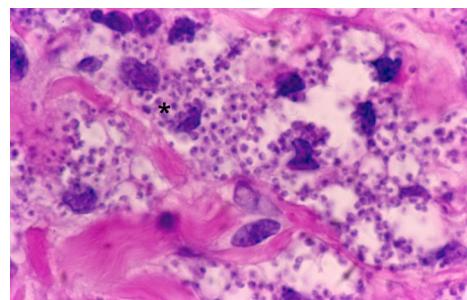
Histologic examination is an important diagnostic method. A punch or incisional/excisional biopsy specimen should be obtained and should include the ulcer or nodule border with both affected and unaffected tissue. In 1 study, direct microscopic

Table V. Histologic patterns suggestive of leishmaniasis

Type	Frequency pattern observed	Histologic findings
1	45%	Abundant amastigotes
2	27.5%	Admixture of macrophages, polymorphonuclear neutrophils, and plasma cells with necrosis
3	15%	Early granuloma formation with focal collection of epithelioid cells, lymphocytes, and a few plasma cells
4	5%	Well-formed epithelioid granuloma in the dermis with Langerhans type giant cells, lymphocytes, and epithelioid cells

**Fig 2.** Staining of a nodule on the forearm reveal numerous round, basophilic intracellular amastigotes with kinetoplasts, indicative of leishmaniasis. (Hematoxylin–eosin stain; original magnification: $\times 40$.)

examination of the biopsy specimen, identifying features suggestive of leishmaniasis, had a sensitivity of 59% in cases of Old World cutaneous leishmaniasis.^{22,23} Even with visualization of amastigotes—the so-called Leishman–Donovan bodies, which have a sensitivity of 50% to 70%—a species-specific diagnosis cannot be ascertained. Another study histologically evaluated 40 biopsy specimens from patients with cutaneous leishmaniasis and identified 4

**Fig 3.** Higher power required to visualize amastigotes in Fig 2. Staining of a nodule on the forearm shows numerous round, basophilic intracellular amastigotes with kinetoplasts (asterisk), indicative of leishmaniasis. (Hematoxylin–eosin stain; original magnification: $\times 1250$.)

histologic patterns based upon abundant macrophages, infiltrate, or stages of granuloma formation²⁴ (Table V). In acute cutaneous leishmaniasis, the epidermis may feature hyperplasia and ulceration. In the early course of disease, there is inflammation with a dense and diffuse dermal infiltrate, primarily of macrophages, which rarely may have a narrow area of uninvolved papillary dermis, referred to as a Grenz zone, between the dermal infiltrate and epidermis. Lymphocytes, plasma cells, and macrophages may also be present in the dermis with organisms predominantly in the macrophages.²⁵ Dense dermal infiltrates often lead to the destruction of adnexal structures. In about 30% of cases, epithelioid cell granulomas with giant cells and a rim of lymphocytes will develop in patients with acute cutaneous leishmaniasis, a finding associated with a good response to treatment and resolving ulceration. Dermal connective tissue with collagen degeneration or palisading around areas of necrosis is usually present.²⁵ In late stages of the lesion, a large number of plasma cells are typically present.²⁶ Even after treatment and clinical cure, patients may still show a moderate inflammatory process, but with elevated levels of the antiinflammatory cytokines interleukin-4 and interleukin-10.²⁷

An important step in histopathologic analysis is searching for amastigotes within macrophages, usually best found beneath the epidermis.²⁸ Each amastigote measures 2 to 4 μm in diameter, so tiny as to require high power magnification to visualize, is a dull blue-gray color with hematoxylin–eosin staining, and is found in clusters in the cytoplasm of dermal macrophages²⁹ (Figs 2–4). In addition to dermal macrophages, the other cell line capable of harboring *Leishmania* parasites is the epidermal Langerhans cell, which migrates from the epidermis to the site of infection in the dermis.³⁰ In chronic relapsing cutaneous leishmaniasis, also referred to as

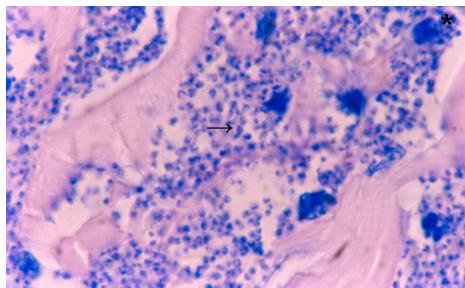


Fig 4. Higher power view of the patient seen in Fig 2. Staining of a nodule on the forearm reveals numerous round, basophilic intracellular amastigotes with kinetoplasts (*asterisks*) and extracellular amastigotes (*arrow*), indicative of leishmaniasis. (Giemsa stain; original magnification: $\times 1250$.)

leishmania recidivans, infections occur within a scar from a previous primary acute cutaneous leishmanial infection. This produces variable epidermal changes and pseudoepitheliomatous hyperplasia, which may be seen if no Grenz zone is present. The epidermis may also have hydropic degeneration of the basal cell layer and a loss of pigment with an extensive lymphocytic superficial and deep dermal infiltrate. The loss of elastic fibers, corresponding with clinical scarring, may be highlighted with an elastic stain.²⁶ Few amastigotes are present in chronic relapsing cutaneous leishmaniasis, making diagnosis by histology difficult.

Microscopic examination of diffuse cutaneous leishmaniasis, most commonly caused by *Leishmania mexicana amazonensis* in the New World and *Leishmania aethiopica* in the Old World, has certain distinct characteristics. A diffuse infiltrate of amastigote-containing macrophages is visible in the dermis.²⁶ Leishmaniasis macrophages that are heavily parasitized have a large vacuole in the cytoplasm with few surrounding lymphocytes, typically noted in patients with an early immune response or anergic diffuse cutaneous leishmaniasis.^{31,32} A mixed inflammatory infiltrate without necrosis is also present, as are nonnecrotic macrophage granulomas with surrounding lymphocytes and plasma cells.^{29,31}

Culture

Key points

- Culture may be challenging to perform, because *Leishmania* organisms are fastidious
- It is the best way to isolate parasites
- Specialized media is required
- In the United States, the Centers for Disease Control and Prevention provides Roswell Park Memorial Institute media for *Leishmania* inoculation, which can then be returned to the Centers for Disease Control

and Prevention for culture and molecular analysis

Culture is not easy to perform, but is the best method to isolate parasites. Material may be obtained from scrapings, aspiration, or a punch biopsy specimen. The most rapid and simplest method used for diagnosis is dermal scrapings, which may be employed for slide evaluation or for culture. In 1 study, the yield was not dependent upon the area of the ulcer used for scraping, whether the center of the ulcer or its raised border.³³ Another method of detection is fine-needle aspiration cytology. This method involves drawing up 0.1 mL of preservative-free sterile 0.9% saline into a 1.0- to 3.0-mL syringe, aspirating tissue from the raised border of the ulcer with a 23- to 27-gauge needle, and examining the tissue for parasites on a leishmanial culture medium.²⁰ One study showed a 41.3% positive rate for it compared with a 34.8% positive rate for dermal scrapings.³⁴ In addition, fine-needle aspiration cytology is preferred because it has a lower risk of culture contamination than dermal scrapings.³⁴

Several different culture media have been used to isolate *Leishmania*, including NNN medium containing sodium chloride in blood agar,³⁵ Evans' modified Tobie's medium containing fetal calf blood serum, L-proline and antibiotics, and Schneider insect medium of salts, sugars, supplements, amino acids, and organic acids.^{36,37} RPMI media, which may be requested from the CDC before obtaining tissue, contains several nutrients necessary for growth of the fastidious *Leishmania* organisms. These cultures, which may be sent at room temperature in the overnight mail to the CDC for growth on NNN blood-slants overlay with RPMI media, may be positive in 3 to 8 days, but it may take up to 4 weeks to obtain species identification.¹⁸ In 1 study, cultures were positive in 83% of cases in which ≥ 1 amastigote was seen on 400 oil-immersion fields and in 27% of cases with a negative microscopic examination.³³ Animal inoculation, most commonly hamsters and mice, may be used to culture *Leishmania* in vivo, but this method is not practical for routine diagnosis. The detection level is a little higher by culturing samples (44–58%) than by inoculation into hamsters (38–52%).^{38,39}

Leishmaniasis tests

The patient's cell-mediated immune response may be measured using the leishmanin (Montenegro) skin test.⁴⁰ An intradermal injection of *Leishmania* antigen, phenol-killed amastigotes, is used to detect cell-mediated immunity.⁴¹ A response should be elicited

and measured after 48 to 72 hours, much like the tuberculin skin test.^{29,42} This test does not differentiate between past and present infection. Moreover, active visceral leishmaniasis, PKDL, and diffuse cutaneous leishmaniasis are characterized by a negative skin test.^{43,44} One study found that only 51.6% of patients infected with *L amazonensis* had positive skin tests, possibly because of immunoinhibition by the parasite itself, much like that seen in visceral leishmaniasis caused by *Leishmania chagasi*.⁴⁴ In endemic areas, positive skin tests may occur because of subclinical infection, even in patients without a history of leishmaniasis. The leishmanin skin test is used as a marker for immunity against cutaneous leishmaniasis. However, the leishmanin skin test conversion reaction may only be a marker for partial immunity towards leishmaniasis.⁴⁵ A decreased responsiveness in the leishmanin skin test in the sporotrichoid type of cutaneous leishmaniasis may be evident compared to the lupoid type.⁴⁶

Species identification

Other diagnostic modalities available include serologic assays, isoenzyme analysis, monoclonal antibody analysis, and the use of DNA probes with PCR studies. The latter 3 are capable of species determination and are currently available at only a few centers worldwide.¹⁸ PCR is used to amplify the amount of kinetoplast DNA, portions of which are unique to each species of Leishmania.⁴⁷ DNA fragments are then hybridized to known species-specific probes, which results in detection rates of 97% even when the initial tissue sample contains few amastigotes.⁴⁷ Determining the specific species is important because treatment and prognosis vary for each species. The CDC provides species identification via PCR, which is more sensitive and rapid than isoenzyme analysis of cultured parasites on submitted tissue specimens and has shown reliability in this approach—with the exception being between *L infantum* and *L chagasi*, species that some authors believe to be synonymous.⁴⁸ This method is currently being adapted for field use, with the initial results being encouraging.⁴⁹ PCR studies are also being used to quantify Leishmania organisms, which can be utilized as a diagnostic and follow-up measurement.⁵⁰ Additional studies need to be performed to evaluate the specificity of PCR studies for their ability to differentiate Leishmania species and subspecies.⁵¹

IMMUNOPROPHYLAXIS

Key points

- **Leishmania evades the immune system by inhibiting phagolysosome biogenesis**

- **Intentional infection on unexposed skin may prevent disfiguring facial lesions**
- **Live organism vaccination is still practiced in rural areas and has been a formal program in a few countries**
- **Killed parasite vaccines are not effective in leishmaniasis prevention**

Leishmania is known to have many virulence factors enhancing infection and its spread. Metalloprotease GP63 is a highly active protease produced by Leishmania that rapidly acts on a wide range of host cells and causes weakening of the macrophage response.⁵² Leishmania is taken up by phagosomes but evades immune recognition by inhibiting phagolysosome biogenesis and altering the phagosome's degradative properties.⁵³

Intentional infection on unexposed areas of the skin may prevent disfiguring facial lesions.⁵⁴ Use of a live vaccine, such as 0.1 mL containing approximately 1.5 million flagellates, produces an artificially induced sore.⁵⁵ The sore typically consists of a painless, pea-sized, bluish red papule lasting for 3 to 6 months, although a small ulcer may occur because of trauma.⁵⁵ The injection site is high on the thigh, which not only conceals the resulting scar, but also reduces the prevalence of human reservoirs because the sores are not accessible to sandflies.⁵⁵ A live vaccine, formerly used in Russia, Iran, and Israel and currently only employed in Uzbekistan,⁵⁶ has been found to be effective in infants and children. In 1 study, lasting immunity was seen in 5 vaccinated infants. However, 6 infants born during the sandfly season—April to November in the Middle East—who were therefore not vaccinated, developed multiple sores on the body and face.⁵⁵ The incubation period for artificially induced sores was usually between 2 and 7 months, but ranged from a few weeks to years.⁵⁷ The variation in incubation time was dependent on the size of inoculum, depth of inoculation, and susceptibility of the recipient.⁵⁷ There is an association with certain human leukocyte antigen (HLA) genes that increases or decreases susceptibility to cutaneous leishmaniasis. Some class I and II HLA genes appear to protect against clinical manifestations of cutaneous leishmaniasis. Investigation of HLA gene protection may lead to the development of future prophylactic or therapeutic interventions for cutaneous leishmaniasis.⁵⁸ Moreover, although immunity may be lifelong, it was not complete until the sore had healed.^{55,57,59} The prepared live vaccine was only viable for 17 days when stored at room temperature, after which it was no longer infective.⁶⁰ Proper use of live vaccines may reduce the incidence of natural infection in hyperendemic areas. The

effective live vaccines led to development of killed parasite vaccines. Although there are conflicting results, most conclude that killed vaccines are ineffective in preventing naturally acquired cutaneous leishmaniasis.⁶¹ Modified live-attenuated vaccines, recombinant antigens, and sandfly saliva proteins are candidate mechanisms that are currently being tested in animal models and humans in hopes of preventing leishmaniasis.⁶²⁻⁶⁴

More recently, partially purified promastigote fractions have appeared effective for vaccination against cutaneous and American cutaneous leishmaniasis.^{65,66} In addition, a recombinant Bacillus Calmette-Guérin vaccine expressing the Leishmania surface proteinase gp63 has proven effective in murine models in stimulating the T_H1 arm of T-helper cells, the latter being responsible for macrophage activation and subsequent parasite destruction.^{67,68} A cluster randomized control study evaluated the effectiveness of a 2-dose killed *L amazonensis* vaccine regimen to prevent American cutaneous leishmaniasis in southeast Brazil.⁶⁹ Results include a reduction in the incidence of cutaneous leishmaniasis in that endemic area. Large-scale studies and human testing are necessary to ascertain the true efficacy of these vaccines.

TREATMENT

Key points

- **Systemic treatment is indicated if the lesions are large, multiple, affect the joints, hands, or feet, or the patient is immunosuppressed**
- **Intralesional antimonial drugs are less toxic than systemic therapy**
- **Liposomal amphotericin B is used in the developed world because it reduces hospitalization stays**
- **Sensitivity to treatment varies by nation and region**

The numerous local and systemic treatments available for leishmaniasis are indicative of the difficulty in finding a successful remedy (Table VI). Systemic treatment is indicated in cases with multiple or large (>4 cm) lesions, presence on the hands or feet, when the face or joints are affected, or in immunosuppressed patients.¹⁰³ About two-thirds of patients with cutaneous leishmaniasis can be cured without systemic therapy.¹⁰⁴ Antimonial drugs were first used at the beginning of the 20th century and are still considered first-line treatment against most forms of leishmaniasis.^{105,106} There has been increasing resistance to antimonial drugs in some endemic areas, limiting their efficacy.¹⁰⁷ With an increase in resistance, the ordinary treatment regimens have

changed to a more species-specific solution when possible.¹⁰⁸ PCR studies allow species identification in as little as 24 hours, facilitating initiation of treatment with the most efficacious drug.¹⁰⁹⁻¹¹¹ With an increase in international travel, it is important to determine the species of leishmaniasis and be cautious of treating based solely on the most prevalent species in the area visited.¹¹² Two pentavalent antimony products available in the USA only from CDC are sodium stibogluconate and meglumine antimoniate. The recommended dosage for both is 20 mg/kg/day for 20 days in cutaneous leishmaniasis and for 28 to 30 days in mucocutaneous and visceral leishmaniasis^{113,114}; this is more efficacious than older lower-dosage regimens without significantly increasing toxicity. Longer durations of therapy have not shown increased efficacy.¹¹⁵ Unfortunately, pentavalent antimonial drugs are most efficiently administered parenterally, making treatment expensive and difficult in rural endemic areas. In addition, antimonial therapy has side effects, with cardiac conduction abnormalities and elevated serum transaminase and pancreatic enzyme levels being among the most serious.¹¹⁴ Because of the route of administration, side effect profile, and developing resistance to antimonial drugs, the search for other treatments has been widespread.

Topical. Topical treatment for New World cutaneous leishmaniasis consists of 15% paromomycin/12% methylbenzethonium chloride ointment applied once a day for 20 days.⁷⁰ The healing rate was 76% as compared to 9% in the untreated group. When combined with 10 days of parenteral meglumine antimoniate, the cure rate was 90%. Paromomycin with gentamicin and paromomycin alone has been used to treat ulcerative *L major* in 81% and 82% of patients, respectively.⁷² Topical therapy employed twice a day for 80 days has been effective in the treatment of chronic relapsing cutaneous leishmaniasis.¹¹⁶ This topical formulation is easy to administer. Its side effects include pruritus, burning, and vesicle formation.⁷¹ An 8-week course of topical imiquimod 3 times per day has been used to treat *L infantum* that was unresponsive to 3 mg/kg/day for 13 days of intravenous liposomal amphotericin B.⁷³ A trial of topical amphotericin B has shown some efficacy against *L major* in Israel.⁷⁴

Intralesional. The use of intralesional antimonial drugs offers the benefits of antimonial therapy while reducing the toxicity of systemic therapy.^{117,118} In adults with Old World cutaneous leishmaniasis, cure rates have been reported as high as 95% when treated with 0.2 to 0.4 mL of sodium stibogluconate intradermally 3 times per week for 2 months.⁷⁵ In Israeli children, intralesional sodium stibogluconate

Table VI. Treatments for leishmaniasis

Medication	Dosing	Leishmania species	Clinical efficacy	References
Topical				
15% paromomycin/12% methylbenzethonium chloride	To lesion daily × 20 days	New World cutaneous leishmaniasis	76%	Krause and Kroeger ⁷⁰
15% paromomycin/12% methylbenzethonium chloride combined with parenteral meglumine antimoniate	Topical ointment × 20 days and 10 days IV antimony	New World cutaneous leishmaniasis	90%	Krause and Kroeger ⁷⁰ and Soto et al ⁷¹
Paromomycin/gentamicin	BID × 20 days	Ulcerative <i>L major</i> in Tunisia	81%	Ben Salah et al ⁷²
Paromomyciin	BID × 20 days	Ulcerative <i>L major</i> in Tunisia	82%	Ben Salah et al ⁷²
Imiquimod	TID × 8 weeks	<i>L infantum</i>	1 of 1 (case report)	Hervas et al ⁷³
Ethanolic amphotericin B (5%)	2-5 gtts per each lesion TID ×	<i>L major</i> in Israel	50%	Vadry et al ⁷⁴
Intralesional				
Sodium stibogluconate	0.2-0.4 mL TIW × 5 wks	Old World cutaneous leishmaniasis	95%	Kellum ⁷⁵
Sodium stibogluconate or meglumine antimoniate	20 mg/kg/day × 20 days	Old and New World cutaneous, mucocutaneous, and visceral	94%	Velez et al ⁷⁶
Pentamidine	300 mg weekly × 3 wks 2 mg/kg daily × 7 days	Surniam <i>L braziliensis</i> in Peru	87.2% 35%	Lai A Fat et al ⁷⁷ Andersen et al ⁷⁸
Intramuscular				
Pentamidine	4 mg/kg every 72 hrs × 3 doses 3 mg/kg/d QOD	<i>L v guyanensis</i> Colombia	58.1% 96%	Neves et al ⁷⁹ Soto ⁸⁰
Meglumine antimoniate	15 mg/kg/day × 20 days	<i>L v guyanensis</i>	55.5%	Neves et al ⁷⁹
Oral				
Miltefosine	2.5 mg/kg/day × 28 days 133-150 mg/day × 3-4 wks 2.5 mg/kg/day × 6 wks 2.5 mg/kg/day × 28 days	Bolivia Colombia <i>L braziliensis</i> in Bolivia <i>L v panamensis</i> in Guatemala <i>L v braziliensis</i> in Guatemala <i>L mexicana mexicana</i> in Guatemala <i>L v panamensis</i> in Colombia <i>L major</i> in Iran <i>L v guyanensis</i>	88% 94% 75% 90% 33% 60% 91% 81.3% 53.6%	Soto et al ⁸¹ Soto et al ⁸² Soto and Toledo ⁸³ Soto et al ⁸⁴ Soto et al ⁸⁴ Soto et al ⁸⁴ Soto et al ⁸⁴ Mohebali et al ⁸⁵ Chrusciak-Talhari et al ⁸⁶

Ketoconazole	600 mg/day × 28 days	<i>L braziliensis panamensis</i> <i>L braziliensis</i> in Guatemala Old World <i>L mexicana</i> in Guatemala <i>L mexicana</i> in Belize Iran India <i>L tropica</i> <i>L mexicana</i> <i>L panamensis</i> <i>L donovani</i>	76% 30% 80% 89% 100% 59% 70% 1 of 1 (case report) 1 of 1 (case report) 33% 87%	Saenz et al ⁸⁷ Navin et al ⁸⁸ Alsaleh et al ⁸⁹ Navin et al ⁸⁸ Jolliffe ⁹⁰ Nassiri-Kashani et al ⁹¹ Dogra and Saxena ⁹² Barzilai et al ⁹³ Baum and Berens ⁹⁴ Velez et al ⁷⁶ Jha et al ⁹⁵
Itraconazole	800 mg/day × 28 days 200 mg/day × 8 wks 4 mg/kg/day × 6 wks			
Allopurinol	300 mg/day × 3 mo 300 mg/TID × 6 wks 100 mg QID × 28 days			
Sitamaquine	1.5-2.5 mg/kg/day × 28 days			
Intravenous				
Sodium stibogluconate or meglumine antimoniate	20 mg/kg/day × 20 days for cutaneous leishmaniasis; × 30 days for mucocutaneous and visceral leishmaniasis	Old and New World cutaneous, mucocutaneous, visceral	>90%	Soto et al ⁸⁴
Sodium stibogluconate	20 mg/kg × 21 days	<i>L v braziliensis</i> in Bolivia	70%	Solomon et al ⁹⁶
Liposomal amphotericin B or amphotericin B deoxycholate	10 mg/kg once or 1 mg/kg × 15 alternate-day	Old World visceral	100%; 98%	Sundar et al ⁹⁷
Liposomal amphotericin B	3 mg/kg/day × 7 days followed by 3 mg/kg × BIW × 3 weeks 3 mg/kg × 5 days with 6th dose on day 10	<i>L v braziliensis</i>	1 of 1 (case report)	Brown et al ⁹⁸
Meglumine antimoniate	20 mg (Sb)/kg/day × 20 days	<i>L v braziliensis</i> in Bolivia	85%	Solomon et al ⁹⁶
Pentamidine	2 mg/kg QOD × 7 doses	<i>L v braziliensis</i> in Peru <i>L v guyanensis</i> in Brazil <i>L v braziliensis</i> in Peru	75% 71.4% 35%	Andersen et al ⁷⁸ Chrusciak-Talhari et al ⁸⁶ Andersen et al ⁷⁸
Physical				
Cryotherapy	2-mm margins × 1-4 weeks	Old World	30-84%	Mosleh et al ⁹⁹
CO ₂ slush	1 min to lesion, repeat monthly if needed	Old World	>90% with 1-2 applications	Al-Qubati et al ¹⁰⁰ and Junaid ¹⁰¹
Radiofrequency-induced heat therapy	55°C × 5 min 50°C × 30 sec	Old World <i>L tropica</i>	90% 69%	Junaid ¹⁰¹ Reithinger et al ¹⁰²

BID, Two times a day; BIW, two times a week; IV, intravenous; QID, four times a day; QOD, every other day; TID, three times a day.

had a cure rate of 66.6% for nonfacial cutaneous leishmaniasis lesions caused by *L tropica*.¹¹⁹ Other advantages of this technique include reduced cost and rapid response to treatment.^{75,120} The recurrence rate was only 4% with approximately 15 injections.¹²⁰ This technique has not been sufficiently tested in the New World species.¹²¹

Subcutaneous. Recently, different subcutaneously injected liposomal formulations of antileishmanial drugs have been prepared to determine effectiveness of reducing amastigote counts and lesion size in *L major*. These formulations included sodium stibogluconate, meglumine antimoniate, miltefosine, and paromycin; however, only the formulations with oral miltefosine had significant therapeutic effects.^{122,123}

Intramuscular. Although painful, intramuscular pentavalent antimonial drugs have been used in the treatment of both Old and New World leishmaniasis. Pentamidine, a antimicrobial medication employed to prevent and treat *Pneumocystis pneumonia*, has been utilized to treat New World species of leishmaniasis, yielding positive results in Surinam and Colombia, but less success in Peru.^{77,78,80} *Leishmania (Viannia) guyanensis* has shown <60% efficacy to both intramuscular pentamidine and meglumine antimoniate.⁷⁹

Oral. Oral miltefosine, a phosphorylcholine ester of hexadecanol originally used to treat cancer, has been shown as efficacious in treating both Old and New World cutaneous and visceral leishmaniasis.¹²⁴ A Colombian study of oral miltefosine reported a dose-dependent cure rate of 89% to 100% for cutaneous leishmaniasis treated with 133 to 150 mg/day for 4 weeks.⁸²⁻⁸⁴ The cure rates for *Leishmania (Viannia) braziliensis* were 88% with 2.5 mg per kg per day for 28 days of oral miltefosine and 94% with 20 mg per kg per day for 20 days of intramuscular antimony for cutaneous leishmaniasis.^{81,125} A large, placebo-controlled study of oral miltefosine (2.5 mg/kg for 6 weeks) had a cure rate of 75% for *L braziliensis* in Bolivia.¹²² A study to treat cutaneous leishmaniasis in Colombia and Guatemala found that species sensitivity to treatment varied by country.^{83,126} In Guatemala, *Leishmania (Viannia) panamensis* had a cure rate >90% with oral miltefosine, but only 33% for *L V braziliensis* and 64% for *L mexicana mexicana*. In Colombia, oral miltefosine had a cure rate of 91% for *L V panamensis*.^{84,127} In Iran, the miltefosine cure rate for *L major* is 81.3%.⁸⁵ Ketoconazole and fluconazole have also been tried in lieu of parenteral antimonial drugs. Ketoconazole (600 mg/day for 28 days) has a comparable cure rate of 76%, compared with parenteral pentavalent antimony for *Leishmania braziliensis panamensis*

cutaneous leishmaniasis, a subspecies of *L braziliensis* found in Panama.⁸⁷ However, the dose of sodium stibogluconate given in this comparison study averaged only 13 mg per kg, which is lower than the recommended 20 mg per kg.^{87,128} In Guatemala, ketoconazole 600 mg per day for 28 days had only a 30% cure rate against *L braziliensis*.⁸⁸ The success of oral antifungals in leishmaniasis was reinforced by another study showing a 80% cure rate of Old World species with 600 mg ketoconazole daily for 4 to 6 weeks.⁸⁹ Ketoconazole's effectiveness is of particular interest because it has been shown to have activity toward *L mexicana*, which is notorious for resistance to antimony treatment.⁹⁰ Recent studies using itraconazole to treat Old World leishmaniasis have documented cure rates ranging from 55% to 78%.^{91,92,129} Another oral agent used is allopurinol, which inhibits purine anabolism in Leishmania and is less expensive and less toxic than the antimonials.¹³⁰ There are cases showing success with 300 mg per day for 3 months for the treatment of *L tropica* cutaneous leishmaniasis and 300 mg 3 times per day for 6 weeks for *L mexicana*.^{93,94} However, allopurinol has been ineffective against *L panamensis*.⁷⁶ In India, visceral leishmaniasis from *Leishmania donovani* has been successfully treated with sitamaquine, but 8% of participants had renal damage.⁹⁵

Intravenous. Despite the advent of medications such as amphotericin B, miltefosine, and pentamidine, pentavalent antimony remains the most commonly used treatment for New World leishmaniasis. Antimony had shown superior efficacy compared to pentamidine in the treatment of Peruvian *L braziliensis*⁷⁸ and superior efficacy to miltefosine for *L V guyanensis* in Brazil.⁸⁶ Amphotericin B has been used to treat leishmaniasis in some parts of the world, especially where antimonial resistance is widespread.¹³¹ The drug increases the permeability of the cell membrane of the parasite and promotes an ion influx, leading to the death of promastigotes and amastigotes.¹³² In India, liposomal amphotericin B was equally efficacious as traditional amphotericin B deoxycholate, with a 100% cure rate after a single infusion.⁹⁷ Liposomal amphotericin B has become the treatment of choice in the developed world because it reduces the duration of inpatient stays.¹³³ There has been successful treatment of cutaneous *L braziliensis*, which is known to have a high resistance to antimonial drugs, with a regimen of 3.125 mg per kg per day for 7 days, then 3.125 twice weekly for 3 weeks of intravenous liposomal amphotericin B.⁹⁸ Other studies have shown efficacy with regimens ranging from 3 to 5 mg per kg per day for 10 days to 2 months.^{96,98,134-140} Liposomal amphotericin B, in a



Fig 5. Cryoslush used in Yemen to treat Old World leishmaniasis.



Fig 6. Disfiguring scars created by traditional healer leishmaniasis treatment.

total dose of 15 to 20 mg per kg, was efficacious, with a very low rate of adverse reactions.¹⁴¹ Amphotericin B is predominately used in developed areas because monitoring for side effects is available. Most commonly, renal function disturbances, anemia, thrombocytopenia, and neurologic disorders, such as visual disturbances and hearing loss, are seen.¹⁴² Central nervous system toxicity may occur after intravenous liposomal amphotericin B has been administered at 3 mg per kg per day for 7 days.¹⁴³

Physical. Several physical modalities used include cryotherapy, local heat, surgery, curettage and electrodesiccation, and CO₂ laser.¹⁴⁴ Cryo-therapy entails freezing the thermosensitive leishmanial lesion until 2-mm margins are obtained, which requires 30 to 60 seconds.¹⁴⁵ With Old World cutaneous leishmaniasis, there was an 84% cure rate with 4 weekly treatment sessions.⁹⁹ However, there are reports of cure rates as low as 30% with cryotherapy.¹⁴⁴ Cryotherapy is expensive; however, Al-Qubati et al¹⁰⁰ described CO₂ slush use for cryosurgery as cost-effective, efficacious, and simple-to-use in resource-poor areas (Fig 5). The utilization of radiofrequency-

induced heat therapy (RFHT) to raise the skin temperature to 55°C for 5 minutes has shown efficacy in treating Old World cutaneous leishmaniasis.^{101,144} Using this technique, it was found that <10% of lesions required a second treatment.¹⁰¹ Moreover, treating 1 lesion invoked an immune response, which resulted in healing of other lesions within 5 to 6 weeks.¹⁰¹ Use of RFHT in *L tropica* had a 69% cure rate in Afghanistan.¹⁰² However, long-term recurrence with RFHT is still unstudied. Its use is limited by expense and unavailability in endemic areas.

In general, no single therapy is 100% effective for leishmaniasis. Antimonial compounds still remain the first-line treatment for cutaneous leishmaniasis caused by *L braziliensis*, mucocutaneous leishmaniasis, and PKDL. Cutaneous disease caused by *L mexicana* may require alternate therapy, such as oral ketoconazole. Old World leishmaniasis is usually self-healing and is best managed by local measures. Potential antileishmanial compounds that have shown success in rodent models include arylimidamides,¹⁴⁶ oral amphotericin B,¹⁴⁷ hydroxybibenzyl compounds,¹⁴⁸ peganine hydrochloride,¹⁴⁹ quinolines,¹⁵⁰ and rhodacyanine dyes.¹⁴⁸ All too often, those in developing nations are treated by traditional healers with folk medicines, resulting in disfiguring results (Fig 6). In addition, folk medicine may allow the disease to exacerbate.¹⁰⁰ There is interest in the exploration of medicinal plant extracts to treat leishmaniasis, as opposed to synthetic compounds, in hopes of maintaining efficacy while decreasing toxicity and production costs.^{151,152}

Prevention

Prevention—whether through vaccination, inhibiting parasite transmission, or sandfly avoidance—is the ultimate goal.¹⁵³ A recent study revealed that sandflies consuming yeast or bacteria before Leishmania ingestion were resistant to enteric colonization.¹⁵⁴ This idea may lead to the removal of sandflies as a vector for leishmaniasis. An attenuated parasite vaccine is being developed that still maintains long-term immunity against the organism.⁵⁶ Pretravel advice is desirable for those planning on visiting endemic regions.⁴¹ Although chemoprophylaxis or acceptable immunization is not yet available, there are other ways to decrease the chance of infection. Avoiding outdoor activities is the best preventive measure, but is usually impractical. The use of insect repellent and protective clothing will reduce exposure to sandflies.⁶ In addition, screening and bed nets with sufficiently fine mesh should be used to prevent passage of sandflies, which are approximately one-third the size of mosquitoes.⁶

Sandflies make no sound when they fly. In addition, their bite may be painless, and may therefore go unnoticed. Although sandflies primarily bite at night, they will bite during the day if they are disturbed. Outdoor activity, if possible, should be limited from dusk to dawn; this is when sandflies are the most active. Sandflies' small size allows them to work their way through standard window screens of 1200 holes per inch and even tighter mesh used by the military. Leishmaniasis, one of the "neglected diseases," remains a worldwide health problem with many different and complex clinical presentations. The various modes of treatment reflect the therapeutic challenges posed by this multifaceted disease.

REFERENCES

1. Jacobs B, Brown DL. Cutaneous furuncular myiasis: Human infestation by the botfly. *Can J Plast Surg.* 2006;14:31-32.
2. Robbins K, Khachemoune A. Cutaneous myiasis: a review of the common types of myiasis. *Int J Dermatol.* 2010;49:1092-1098.
3. Sunenshine PJ, Janniger CK, Schwartz RA. Tungiasis. In: Demis DJ, ed. *Clinical Dermatology*. Philadelphia, PA: Lippincott, Williams & Wilkins; 1999:1-10.
4. Goihman-Yahr M. American mucocutaneous leishmaniasis. *Dermatol Clin.* 1994;12:703-712.
5. Aquilar CM, Reigosa A. Leishmaniasis cutánea del pene en un paciente de Venezuela. *Medicina Cutánea Ibero-Latino-Americana.* 1994;22:380-382.
6. Herwaldt BL, Stokes SL, Juranek DD. American cutaneous leishmaniasis in U.S. travelers. *Ann Intern Med.* 1993;118:779-784.
7. Kopterides P, Mourtzoukou EG, Skopelitis E, Tsavaris N, Falagas ME. Aspects of the association between leishmaniasis and malignant disorders. *Trans R Soc Trop Med Hyg.* 2007;101:1181-1189.
8. Control of the leishmaniases. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* 1990;793:1-158.
9. UI Bari A, Raza N. Lupoid cutaneous leishmaniasis: a report of 16 cases. *Indian J Dermatol Venereol Leprol.* 2010;76:85.
10. Pineda JA, Gallardo JA, Macias J, et al. Prevalence of and factors associated with visceral leishmaniasis in human immunodeficiency virus type 1-infected patients in southern Spain. *J Clin Microbiol.* 1998;36:2419-2422.
11. de La Rosa R, Pineda JA, Delgado J, et al. Incidence of and risk factors for symptomatic visceral leishmaniasis among human immunodeficiency virus type 1-infected patients from Spain in the era of highly active antiretroviral therapy. *J Clin Microbiol.* 2002;40:762-767.
12. Convit J, Reyes O, Kerdel F. Disseminated anergic American leishmaniasis; report of three cases of a type clinically resembling lepromatous leprosy. *AMA Arch Derm.* 1957;76:213-217.
13. Niamba P, Goumbri-Lombo O, Traore A, Barro-Traore F, Soudre RT. Diffuse cutaneous leishmaniasis in an HIV-positive patient in western Africa. *Australas J Dermatol.* 2007;48:32-34.
14. Schwartz RA, Goriniene E, Szepietowski JC, et al. Rhinoscleroma. Available at: <http://emedicine.medscape.com/article/1055113-overview>. Accessed May 8, 2014.
15. Davies CR, Kaye P, Croft SL, Sundar S. Leishmaniasis: new approaches to disease control. *BMJ (Clin Res Ed).* 2003;326:377-382.
16. Llambrich A, Zaballos P, Terrasa F, Torne I, Puig S, Malvehy J. Dermoscopy of cutaneous leishmaniasis. *Br J Dermatol.* 2009;160:756-761.
17. Yucel A, Gunasti S, Denli Y, Uzun S. Cutaneous leishmaniasis: new dermoscopic findings. *Int J Dermatol.* 2013;52:831-837.
18. Kalter DC. Laboratory tests for the diagnosis and evaluation of leishmaniasis. *Dermatol Clin.* 1994;12:37-50.
19. Skoryna-Karcz B, Chojecka-Adamska A, Adamski Z. The case of cutaneous leishmaniasis - diagnostic difficulties. *Przegl Dermatol.* 1994;81:544-547.
20. US Centers for Disease Control and Prevention website. Practical guide for specimen collection and reference diagnosis of leishmaniasis. Available at: http://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis.pdf. Accessed October 21, 2014.
21. de Almeida ME. Leishmaniasis. Correspondence to MZ Handler. June 27, 2014.
22. Al-Huchemi SN, Sultan BA, Al-Dhalimi MA. A comparative study of the diagnosis of Old World cutaneous leishmaniasis in Iraq by polymerase chain reaction and microbiologic and histopathologic methods. *Int J Dermatol.* 2009;48:404-408.
23. Vega-Lopez F. Diagnosis of cutaneous leishmaniasis. *Curr Opin Infect Dis.* 2003;16:97-101.
24. Venkataram M, Moosa M, Devi L. Histopathological spectrum in cutaneous leishmaniasis: a study in Oman. *Indian J Dermatol Venereol Leprol.* 2001;67:294-298.
25. Biddlestone LR, Hepburn NC, McLaren KM. A clinico-pathological study of cutaneous leishmaniasis in British troops from Belize. *Trans R Soc Trop Med Hyg.* 1994;88:672-676.
26. Mehregan DR, Mehregan DA, Mehregan AH. Histopathology of cutaneous leishmaniasis. *Gulf J Dermatol Venereol.* 1997;4:1-9.
27. Viana AG, Mayrink W, Fraga CA, et al. Histopathological and immunohistochemical aspects of American cutaneous leishmaniasis before and after different treatments. *An Bras Dermatol.* 2013;88:32-40.
28. Singh A, Ramesh V. Histopathological features in leprosy, post-kala-azar dermal leishmaniasis, and cutaneous leishmaniasis. *Indian J Dermatol Venereol Leprol.* 2013;79:360-366.
29. Farah FS, Klaus SN, Frankenburg S. Protozoan and helminth infections. In: Farah FS, ed. *Dermatology In General Medicine*. New York: McGraw-Hill; 1993:2772-2777.
30. Blank C, Fuchs H, Rappersberger K, Rollinghoff M, Moll H. Parasitism of epidermal Langerhans cells in experimental cutaneous leishmaniasis with *Leishmania major*. *J Infect Dis.* 1993;167:418-425.
31. Uthman MA, Satir AA, Tabbara KS. Clinical and histopathological features of zoonotic cutaneous leishmaniasis in Saudi Arabia. *J Eur Acad Dermatol Venereol.* 2005;19:431-436.
32. Barral A, Costa JM, Bittencourt AL, Barral-Netto M, Carvalho EM. Polar and subpolar diffuse cutaneous leishmaniasis in Brazil: clinical and immunopathologic aspects. *Int J Dermatol.* 1995;34:474-479.
33. Navin TR, Arana FE, de Merida AM, Arana BA, Castillo AL, Silvers DN. Cutaneous leishmaniasis in Guatemala: comparison of diagnostic methods. *Am J Trop Med Hyg.* 1990;42:36-42.
34. al-Jitawi SA, Farraj SE, Ramahi SA. Conventional scraping versus fine needle aspiration cytology in the diagnosis of cutaneous leishmaniasis. *Acta Cytol.* 1995;39:82-84.
35. Atlas RM, Snyder JW. *Handbook of Media for Clinical Microbiology*. Boca Raton, FL: CRC Press; 2006. pp. 337-340.

36. Echalier G. *Composition of the body fluid of drosophila and the design of culture media for drosophila cells. Drosophila cells in culture.* San Diego, CA: Academic Press; 1997. pp. 3-23.
37. Ohl CA, Hyams KC, Malone JD, Oldfield E 3rd. Leishmaniasis among Desert Storm veterans: a diagnostic and therapeutic dilemma. *Mil Med.* 1993;158:726-729.
38. Schubach A, Cuzzi-Maya T, Oliveira AV, et al. Leishmanial antigens in the diagnosis of active lesions and ancient scars of American tegumentary leishmaniasis patients. *Mem Inst Oswaldo Cruz.* 2001;96:987-996.
39. Weigle KA, de Dávalos M, Heredia P, Molineros R, Saravia NG, D'Alessandro A. Diagnosis of cutaneous and mucocutaneous leishmaniasis in Colombia: a comparison of seven methods. *Am J Trop Med Hyg.* 1987;36:489-496.
40. Almeida OL, Santos JB. Advances in the treatment of cutaneous leishmaniasis in the new world in the last ten years: a systematic literature review. *An Bras Dermatol.* 2011; 86:497-506.
41. Stockdale L, Newton R. A review of preventative methods against human leishmaniasis infection. *PLoS Negl Trop Dis.* 2013;7:e2278.
42. Battistini G, Herrer A, Liseras J. Presencia de Lectospira batavaiae en el Perú. *Rev Peru Med Exp.* 1945;4:101-116.
43. Neogy AB, Nandy A, Chowdhury AB. Leishmanin test in post—kala-azar dermal leishmaniasis. *Trans R Soc Trop Med Hyg.* 1990;84:58.
44. Silveira FT, Lainson R, Shaw JJ, De Souza AA, Ishikawa EA, Braga RR. Cutaneous leishmaniasis due to *Leishmania (Leishmania) amazonensis* in Amazonian Brazil, and the significance of a negative Montenegro skin-test in human infections. *Trans R Soc Trop Med Hyg.* 1991;85:735-738.
45. Momeni Boroujeni A, Aminjavaheri M, Moshtaghan B, Momeni A, Momeni AZ. Reevaluating leishmanin skin test as a marker for immunity against cutaneous leishmaniasis. *Int J Dermatol.* 2013;52:827-830.
46. Sadeghian G, Ziae H, Bidabadi LS, Nilforoushzadeh MA. Evaluation of leishmanin skin test reaction in different variants of cutaneous leishmaniasis. *Indian J Dermatol.* 2013;58:239.
47. Rodriguez N, Guzman B, Rodas A, Takiff H, Bloom BR, Convit J. Diagnosis of cutaneous leishmaniasis and species discrimination of parasites by PCR and hybridization. *J Clin Microbiol.* 1994;32:2246-2252.
48. de Almeida ME, Steurer FJ, Koru O, Herwaldt BL, Pieniazek NJ, da Silva AJ. Identification of *Leishmania* spp. by molecular amplification and DNA sequencing analysis of a fragment of rRNA internal transcribed spacer 2. *J Clin Microbiol.* 2011;49: 3143-3149.
49. Lopez M, Inga R, Cangalaya M, et al. Diagnosis of *Leishmania* using the polymerase chain reaction: a simplified procedure for field work. *Am J Trop Med Hyg.* 1993;49:348-356.
50. Jara M, Adaui V, Valencia BM, et al. Real-time PCR assay for detection and quantification of *Leishmania* (Viannia) organisms in skin and mucosal lesions: exploratory study of parasite load and clinical parameters. *J Clin Microbiol.* 2013; 51:1826-1833.
51. de Paiva Cavalcanti M, Dantas-Torres F, da Cunha Gonçalves de Albuquerque S, et al. Quantitative real time PCR assays for the detection of *Leishmania (Viannia) braziliensis* in animals and humans. *Mol Cell Probes.* 2013;27:122-128.
52. Olivier M, Atayde VD, Isnard A, Hassani K, Shio MT. Leishmania virulence factors: focus on the metalloprotease GP63. *Microbes Infect.* 2012;14:1377-1389.
53. Matheoud D, Moradin N, Bellemare-Pelletier A, et al. Leishmania evades host immunity by inhibiting antigen cross-presentation through direct cleavage of the SNARE VAMP8. *Cell Host Microbe.* 2013;14:15-25.
54. Manson P. *Oriental Sore.* London, UK: Cassell and Co, Ltd; 1898.
55. Katzenellenbogen I. Vaccination against oriental sore: report of results of five hundred and fifty-five inoculations. *Arch Derm Syphilol.* 1944;50:239-242.
56. Saljoughian N, Taheri T, Rafati S. Live vaccination tactics: possible approaches for controlling visceral leishmaniasis. *Front Immunol.* 2014;5:134.
57. Berberian DA. Cutaneous leishmaniasis (oriental sore): II. incubation period. *Arch Derm Syphilol.* 1944;50:231-232.
58. Ribas-Silva RC, Ribas AD, Dos Santos MC, et al. Association between HLA genes and American cutaneous leishmaniasis in endemic regions of Southern Brazil. *BMC Infect Dis.* 2013; 13:198.
59. Ameen M. Cutaneous leishmaniasis: advances in disease pathogenesis, diagnostics and therapeutics. *Clin Exp Dermatol.* 2010;35:699-705.
60. Berberian DA. Cutaneous leishmaniasis (oriental sore): III. period of infectivity of saline suspensions of *Leishmania tropica* cultures kept at room temperature. *Arch Derm Syphilol.* 1944;50:233.
61. Berberian DA. Cutaneous leishmaniasis (oriental sore): IV. vaccination against oriental sore with suspensions of killed *Leishmania tropica*. *Arch Derm Syphilol.* 1944;50:234-236.
62. Kamhawi S, Belkaid Y, Modi G, Rowton E, Sacks D. Protection against cutaneous leishmaniasis resulting from bites of uninfected sand flies. *Science.* 2000;290:1351-1354.
63. Kubar J, Fragaki K. Leishmania proteins derived from recombinant DNA: current status and next steps. *Trends Parasitol.* 2006;22:111-116.
64. Bogdan C. Leishmaniasis in rheumatology, haematology and oncology: epidemiological, immunological and clinical aspects and caveats. *Ann Rheum Dis.* 2012;71(suppl 2): i60-i66.
65. Monjour L, Monjour E, Vouldoukis I, Ogunkolade BW, Frommel D. Protective immunity against cutaneous leishmaniasis achieved by partly purified vaccine in a volunteer. *Lancet.* 1986;1:1490.
66. Monjour L, Silva OA, Vouldoukis I, et al. Immunoprophylaxis in cutaneous leishmaniasis. *Lancet.* 1992;340:1098-1099.
67. Connell ND, Medina-Acosta E, McMaster WR, Bloom BR, Russell DG. Effective immunization against cutaneous leishmaniasis with recombinant bacille Calmette-Guerin expressing the *Leishmania* surface proteinase gp63. *Proc Natl Acad Sci U S A.* 1993;90:11473-11477.
68. Russo DM, Burns JM Jr, Carvalho EM, et al. Human T cell responses to gp63, a surface antigen of *Leishmania*. *J Immunol.* 1991;147:3575-3580.
69. Mayrink W, Mendonça-Mendes A, de Paula JC, et al. Cluster randomised trial to evaluate the effectiveness of a vaccine against cutaneous leishmaniasis in the Caratinga microregion, southeast Brazil. *Trans R Soc Trop Med Hyg.* 2013; 107:212-219.
70. Krause G, Kroeger A. Topical treatment of American cutaneous leishmaniasis with paramomycin and methylbenzethonium chloride: a clinical study under field conditions in Ecuador. *Trans R Soc Trop Med Hyg.* 1994;88:92-94.
71. Soto J, Hernandez N, Mejia H, Grogli M, Berman J. Successful treatment of New World cutaneous leishmaniasis with a combination of topical paramomycin/methylbenzethonium chloride and injectable meglumine antimonate. *Clin Infect Dis.* 1995;20:47-51.

72. Ben Salah A, Ben Messaoud N, Guedri E, et al. Topical paramomycin with or without gentamicin for cutaneous leishmaniasis. *N Engl J Med.* 2013;368:524-532.
73. Hervas JA, Martin-Santiago A, Hervas D, et al. Old World *Leishmania infantum* cutaneous leishmaniasis unresponsive to liposomal amphotericin B treated with topical imiquimod. *Pediatr Infect Dis J.* 2012;31:97-100.
74. Vardy D, Barenholz Y, Cohen R, et al. Topical amphotericin B for cutaneous leishmaniasis. *Arch Dermatol.* 1999;135: 856-857.
75. Kellum RE. Treatment of cutaneous leishmaniasis with an intralesional antimonial drug (Pentostam). *J Am Acad Dermatol.* 1986;15:620-622.
76. Velez I, Agudelo S, Hendrickx E, et al. Inefficacy of allopurinol as monotherapy for Colombian cutaneous leishmaniasis. A randomized, controlled trial. *Ann Intern Med.* 1997;126: 232-236.
77. Lai A, Fat EJ, Vrede MA, Soetenosojo RM, Lai A, Fat RF. Pentamidine, the drug of choice for the treatment of cutaneous leishmaniasis in Surinam. *Int J Dermatol.* 2002;41: 796-800.
78. Andersen EM, Cruz-Saldarriaga M, Llanos-Cuentas A, et al. Comparison of meglumine antimoniate and pentamidine for peruvian cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2005; 72:133-137.
79. Neves LO, Talhari AC, Gadelha EP, et al. A randomized clinical trial comparing meglumine antimoniate, pentamidine and amphotericin B for the treatment of cutaneous leishmaniasis by *Leishmania guyanensis*. *An Bras Dermatol.* 2011;86: 1092-1101.
80. Soto J, Buffet P, Grogl M, Berman J. Successful treatment of Colombian cutaneous leishmaniasis with four injections of pentamidine. *Am J Trop Med Hyg.* 1994;50:107-111.
81. Soto J, Rea J, Balderrama M, et al. Efficacy of miltefosine for Bolivian cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2008; 78:210-211.
82. Soto J, Toledo J, Gutierrez P, et al. Treatment of American cutaneous leishmaniasis with miltefosine, an oral agent. *Clin Infect Dis.* 2001;33:E57-61.
83. Soto J, Toledo JT. Oral miltefosine to treat new world cutaneous leishmaniasis. *Lancet Infect Dis.* 2007;7:7.
84. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis.* 2004;38:1266-1272.
85. Mohebali M, Fotouhi A, Hooshmand B, et al. Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta Trop.* 2007;103:33-40.
86. Chrusciak-Talhari A, Dietze R, Chrusciak Talhari C, et al. Randomized controlled clinical trial to access efficacy and safety of miltefosine in the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) guyanensis* in Manaus, Brazil. *Am J Trop Med Hyg.* 2011;84:255-260.
87. Saenz RE, Paz H, Berman JD. Efficacy of ketoconazole against *Leishmania braziliensis panamensis* cutaneous leishmaniasis. *Am J Med.* 1990;89:147-155.
88. Navin TR, Arana BA, Arana FE, Berman JD, Chajón JF. Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis.* 1992;165:528-534.
89. Alsaleh QA, Dvorak R, Nanda A. Ketoconazole in the treatment of cutaneous leishmaniasis in Kuwait. *Int J Dermatol.* 1995;34:495-497.
90. Jolliffe DS. Cutaneous leishmaniasis from Belize—treatment with ketoconazole. *Clin Exp Dermatol.* 1986;11:62-68.
91. Nassiri-Kashani M, Firooz A, Khamesipour A, et al. A randomized, double-blind, placebo-controlled clinical trial of itraconazole in the treatment of cutaneous leishmaniasis. *J Eur Acad Dermatol Venereol.* 2005;19:80-83.
92. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol.* 1996;26:1413-1415.
93. Barzilai A, Friedman J, Trau H. Treatment of cutaneous leishmaniasis with allopurinol. *J Am Acad Dermatol.* 1995; 32:518.
94. Baum KF, Berens RL. Successful treatment of cutaneous leishmaniasis with allopurinol after failure of treatment with ketoconazole. *Clin Infect Dis.* 1994;18:813-815.
95. Jha TK, Sundar S, Thakur CP, Felton JM, Sabin AJ, Horton J. A phase II dose-ranging study of sitamaquine for the treatment of visceral leishmaniasis in India. *Am J Trop Med Hyg.* 2005;73: 1005-1011.
96. Solomon M, Pavlitzky F, Barzilai A, Schwartz E. Liposomal amphotericin B in comparison to sodium stibogluconate for *Leishmania braziliensis* cutaneous leishmaniasis in travelers. *J Am Acad Dermatol.* 2013;68:284-289.
97. Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med.* 2010;362:504-512.
98. Brown M, Noursadeghi M, Boyle J, Davidson RN. Successful liposomal amphotericin B treatment of *Leishmania braziliensis* cutaneous leishmaniasis. *Br J Dermatol.* 2005;153: 203-205.
99. Mosleh IM, Geith E, Natsheh L, Schonian G, Abotteen N, Kharabsheh S. Efficacy of a weekly cryotherapy regimen to treat *Leishmania major* cutaneous leishmaniasis. *J Am Acad Dermatol.* 2008;58:617-624.
100. Al-Qubati Y, Janniger EJ, Schwartz RA. Cutaneous leishmaniasis: cryosurgery using carbon dioxide slush in a resource-poor country. *Int J Dermatol.* 2012;51:1217-1220.
101. Junaid AJ. Treatment of cutaneous leishmaniasis with infrared heat. *Int J Dermatol.* 1986;25:470-472.
102. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis.* 2005;40:1148-1155.
103. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis.* 2007;7: 581-596.
104. Morizot G, Kendjo E, Mouri O, et al. Travelers with cutaneous leishmaniasis cured without systemic therapy. *Clin Infect Dis.* 2013;57:370-380.
105. Biagi FF. *La Leishmaniasis Tegumentaria Mexicana y Algunos Datos Médico - Estadísticos de Escárcega*, Camp. Mexico City, Mexico: Universidad Nacional Autonoma de Mexico; 1953.
106. Marsden PD. Current concepts in parasitology. *Leishmaniasis*. *N Engl J Med.* 1979;300:350-352.
107. Kedzierski L. Leishmaniasis. *Hum Vaccin.* 2011;7:1204-1214.
108. Ramanathan R, Talaat KR, Fedorko DP, Mahanty S, Nash TE. A species-specific approach to the use of non-antimony treatments for cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2011;84:109-117.
109. Andrade RV, Massone C, Lucena MN, et al. The use of polymerase chain reaction to confirm diagnosis in skin biopsies consistent with American tegumentary leishmaniasis at histopathology: a study of 90 cases. *An Bras Dermatol.* 2011;86:892-896.
110. Benicio Ede A, Gadelha EP, Talhari A, et al. Combining diagnostic procedures for the management of leishmaniasis

- in areas with high prevalence of *Leishmania guyanensis*. *An Bras Dermatol.* 2011;86:1141-1144.
111. Weirather JL, Jeronimo SM, Gautam S, et al. Serial quantitative PCR assay for detection, species discrimination, and quantification of *Leishmania* spp. in human samples. *J Clin Microbiol.* 2011;49:3892-3904.
 112. Mohammadi AM, Khamesipour A, Khatami A, et al. Cutaneous leishmaniasis in suspected patients referred to the center for research and training in skin diseases and leprosy, Tehran, Iran from 2008 to 2011. *Iran J Parasitol.* 2013;8:430-436.
 113. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg.* 1992; 46:296-306.
 114. Sundar S, Chakravarty J. Leishmaniasis: an update of current pharmacotherapy. *Expert Opin Pharmacother.* 2013;14:53-63.
 115. Franke ED, Llanos-Cuentas A, Echevarria J, et al. Efficacy of 28-day and 40-day regimens of sodium stibogluconate (Pentostam) in the treatment of mucosal leishmaniasis. *Am J Trop Med Hyg.* 1994;51:77-82.
 116. Radentz WH. Leishmaniasis (clinical manifestations, immunologic responses, and treatment). *J Assoc Milit Dermatol.* 1987; 13:15-21.
 117. Soto J, Rojas E, Guzman M, et al. Intralesional antimony for single lesions of Bolivian cutaneous leishmaniasis. *Clin Infect Dis.* 2013;56:1255-1260.
 118. Singh N, Kumar M, Singh RK. Leishmaniasis: current status of available drugs and new potential drug targets. *Asian Pac J Trop Med.* 2012;5:485-497.
 119. Solomon M, Schwartz E, Pavlotsky F, Sakka N, Barzilai A, Greenberger S. Leishmania tropica in children: a retrospective study. *J Am Acad Dermatol.* 2014;71:271-277.
 120. Memişoglu HR, Acar MA, Göyük M, et al. Intralesionale Antimon Behandlung bei kutaner Leishmaniasis. *Hautnah Dermatologie.* 1991;2:97-100.
 121. Murray HW. Leishmaniasis in the United States: treatment in 2012. *Am J Trop Med Hyg.* 2012;86:434-440.
 122. Momeni A, Rasoolian M, Momeni A, et al. Development of liposomes loaded with anti-leishmanial drugs for the treatment of cutaneous leishmaniasis. *J Liposome Res.* 2013;23: 134-144.
 123. Al Qubati Y. Cutaneous leishmaniasis from Yemen: treatment with intralesional injection of sodium stibogluconate with local anesthetic. *Saudi Med J.* 1997;18:433-434.
 124. Croft SL, Sundar S, Fairlamb AH. Drug resistance in leishmaniasis. *Clin Microbiol Rev.* 2006;19:111-126.
 125. Soto J, Rea J, Balderrama M, et al. Efficacy of extended (six weeks) treatment with miltefosine for mucosal leishmaniasis in Bolivia. *Am J Trop Med Hyg.* 2009;81:387-389.
 126. Machado PR, Penna G. Miltefosine and cutaneous leishmaniasis. *Curr Opin Infect Dis.* 2012;25:141-144.
 127. Munoz C, Alzoubi K, Jacobi J, Abed M, Lang F. Effect of miltefosine on erythrocytes. *Toxicol In Vitro.* 2013;27: 1913-1919.
 128. US Food and Drug Administration website. FDA limits usage of Nizoral (ketoconazole) oral tablets due to potentially fatal liver injury and risk of drug interactions and adrenal gland problems. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm362415.htm>. Accessed May 6, 2014.
 129. Van den Enden E, Van Gompel A, Stevens A, et al. Treatment of cutaneous leishmaniasis with oral itraconazole. *Int J Dermatol.* 1994;33:285-286.
 130. LaFon SW, Nelson DJ, Berens RL, Marr JJ. Inosine analogs. Their metabolism in mouse L cells and in *Leishmania donovani*. *J Biol Chem.* 1985;260:9660-9665.
 131. Campos-Munoz L, Quesada-Cortes A, Martin-Diaz MA, Rubio-Flores C, de Lucas-Laguna R. *Leishmania braziliensis*: report of a pediatric imported case with response to liposomal amphotericin B [in Spanish]. *Actas Dermosifiliogr.* 2007;98:42-44.
 132. Ellis M, Bernsen R, Ali-Zadeh H, et al. A safety and feasibility study comparing an intermittent high dose with a daily standard dose of liposomal amphotericin B for persistent neutropenic fever. *J Med Microbiol.* 2009;58:1474-1485.
 133. Wortmann G, Zapor M, Ressner R, et al. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2010;83:1028-1033.
 134. del Rosal T, Artigao FB, Miguel MJ, de Lucas R, del Castillo F. Successful treatment of childhood cutaneous leishmaniasis with liposomal amphotericin B: report of two cases. *J Trop Pediatr.* 2010;56:122-124.
 135. Gunduz K, Afsar S, Ayhan S, et al. Recidivans cutaneous leishmaniasis unresponsive to liposomal amphotericin B (AmBisome). *J Eur Acad Dermatol Venereol.* 2000;14:11-13.
 136. Mirzabeigi M, Farooq U, Baraniak S, Dowdy L, Ciancio G, Vincic V. Reactivation of dormant cutaneous Leishmania infection in a kidney transplant patient. *J Cutan Pathol.* 2006; 33:701-704.
 137. Rapp C, Imbert P, Darie H, et al. Liposomal amphotericin B treatment of cutaneous leishmaniasis contracted in Djibouti and resistant to meglumine antimoniate [in French]. *Bull Soc Pathol Exot.* 2003;96:209-211.
 138. Rongioletti F, Cannata GE, Parodi A. Leishmaniasis due to *L. infantum* presenting as macrocheilitis and responding to liposomal amphotericin B. *Eur J Dermatol.* 2009;19: 281-282.
 139. Perez-Ayala A, Norman F, Perez-Molina JA, Herrero JM, Monge B, Lopez-Velez R. Imported leishmaniasis: a heterogeneous group of diseases. *J Travel Med.* 2009;16: 395-401.
 140. Torre-Cisneros J, Prada JL, Villanueva JL, Valverde F, Sanchez-Guijo P. Successful treatment of antimony-resistant cutaneous leishmaniasis with liposomal amphotericin B. *Clin Infect Dis.* 1994;18:1024-1025.
 141. Balasegaram M, Ritmeijer K, Lima MA, et al. Liposomal amphotericin B as a treatment for human leishmaniasis. *Expert Opin Emerg Drugs.* 2012;17:493-510.
 142. Butsch F, Faulde M, Debus A, Bogdan C, von Stebut E. Two cases of successful treatment of multilesional cutaneous leishmaniasis with liposomal amphotericin B. *J Dtsch Dermatol Ges.* 2013;11:83-85.
 143. Glasser JS, Murray CK. Central nervous system toxicity associated with liposomal amphotericin B therapy for cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2011;84: 566-568.
 144. Koff AB, Rosen T. Treatment of cutaneous leishmaniasis. *J Am Acad Dermatol.* 1994;31:693-708.
 145. Bossiouny A, El Meshad M, Talaat M, Kutty K, Metawaa B. Cryosurgery in cutaneous leishmaniasis. *Br J Dermatol.* 1982; 107:467-474.
 146. Wang MZ, Zhu X, Srivastava A, et al. Novel arylimidamides for treatment of visceral leishmaniasis. *Antimicrob Agents Chemother.* 2010;54:2507-2516.
 147. Wasan KM, Wasan EK, Gershkovich P, et al. Highly effective oral amphotericin B formulation against murine visceral leishmaniasis. *J Infect Dis.* 2009;200:357-360.
 148. Roldos V, Nakayama H, Rolon M, et al. Activity of a hydroxybibenzyl bryophyte constituent against *Leishmania* spp. and *Trypanosoma cruzi*: in silico, in vitro and in vivo activity studies. *Eur J Med Chem.* 2008;43:1797-1807.

149. Khalil T, Misra P, Gupta S, et al. Peganine hydrochloride dihydrate an orally active antileishmanial agent. *Bioorg Med Chem Lett.* 2009;19:2585-2586.
150. Palit P, Paira P, Hazra A, et al. Phase transfer catalyzed synthesis of bis-quinolines: antileishmanial activity in experimental visceral leishmaniasis and in vitro antibacterial evaluation. *Eur J Med Chem.* 2009;44:845-853.
151. Oliveira LF, Schubach AO, Martins MM, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. *Acta tropica.* 2011;118:87-96.
152. Tiuman TS, Santos AO, Ueda-Nakamura T, Filho BP, Nakamura CV. Recent advances in leishmaniasis treatment. *Int J Infect Dis.* 2011;15:e525-e532.
153. Gonzalez U. Cochrane reviews on neglected diseases: the case of cutaneous leishmaniasis. *Cochrane Database Syst Rev.* 2013;3:ED000055.
154. Sant'Anna MR, Diaz-Albiter H, Aguiar-Martins K, et al. Colonisation resistance in the sand fly gut: Leishmania protects *Lutzomyia longipalpis* from bacterial infection. *Parasit Vectors.* 2014;7:329.

Mucocutaneous manifestations of helminth infections

Nematodes

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Learning objectives

After completing this learning activity, participants should be able to describe the cutaneous manifestations of infections by nematodes and identify appropriate therapy.

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In the 21st century, despite increased globalization through international travel for business, medical volunteerism, pleasure, and immigration/refugees into the United States, there is little published in the dermatology literature regarding the cutaneous manifestations of helminth infections. Approximately 17% of travelers seek medical care because of cutaneous disorders, many related to infectious etiologies. This review will focus on the cutaneous manifestations of helminth infections and is divided into 2 parts: part I focuses on nematode infections, and part II focuses on trematode and cestode infections. This review highlights the clinical manifestations, transmission, diagnosis, and treatment of helminth infections. Nematodes are roundworms that cause diseases with cutaneous manifestations, such as cutaneous larval migrans, onchocerciasis, filariasis, gnathostomiasis, loiasis, dracunculiasis, strongyloidiasis, ascariasis, streptocerciasis, dirofilariasis, and trichinosis. Trematodes, also known as flukes, cause schistosomiasis, paragonimiasis, and fascioliasis. Cestodes (tapeworms) are flat, hermaphroditic parasites that cause diseases such as sparganosis, cysticercosis, and echinococcus. (J Am Acad Dermatol 2015;73:929-44.)

Key words: helminth; nematodes; parasite; travel; tropical.

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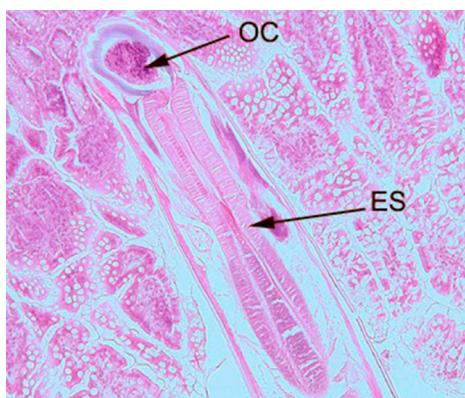


Fig 1. Longitudinal section of an adult hookworm in a bowel biopsy specimen. Note the oral cavity (OC) and esophagus (ES). Courtesy of the Centers for Disease Control and Prevention. (Hematoxylin–eosin stain.)

NEMATODE INFECTIONS

Key points

- Nematode infections are common parasites, with millions of people infected
- Prevalence varies, but increases with poverty and tropical climate
- Control of nematode infection is based on drug treatment, improved sanitation, and education

Nematodes are commonly parasitic to humans, with >60 species known to infect man. Nematodes are elongated with symmetrical bodies that contain an intestinal system and a large body cavity. Dermatologists should be familiar with these infections because of their increased presence in the United States, increased travel, and economic globalization.^{1–7} In this continuing medical education article, we review the nematode infections with important mucocutaneous manifestations.

CUTANEOUS LARVAL MIGRANS

Key points

- Cutaneous larval migrans presents with an erythematous, pruritic eruption and is caused by percutaneous penetration of animal hookworms
- Infection is caused by filariform larvae burrowing through the skin; common places of infection are sand or soil contaminated with animal feces
- The disease is usually self-limited, but patients typically will seek medical treatment
- Ivermectin can be used to shorten the clinical course of disease and prevent superinfection.



Fig 2. Cutaneous larva migrans on the left foot. Note the elevated, serpiginous track of the hookworm. Courtesy of the Centers for Disease Control and Prevention.



Fig 3. Disseminated cutaneous larva migrans.

Cutaneous larval migrans (CLM) usually affects tourists and inhabitants of tropical and subtropical climates, such as the southeastern United States, South America, Southeast Asia, and Africa. CLM is caused by larval migration of animal hookworms, most commonly *Ancylostoma braziliense*, *Ancylostoma ceylanicum*, and *Ancylostoma caninum*.

Life cycle

The life cycle begins as larvae attach to the skin of their definitive animal host (usually nondomesticated cats or dogs), eventually arriving to the pulmonary system. The larvae are subsequently swallowed, entering the gastrointestinal tract. Adult larvae (Fig 1) then shed eggs that are eliminated in

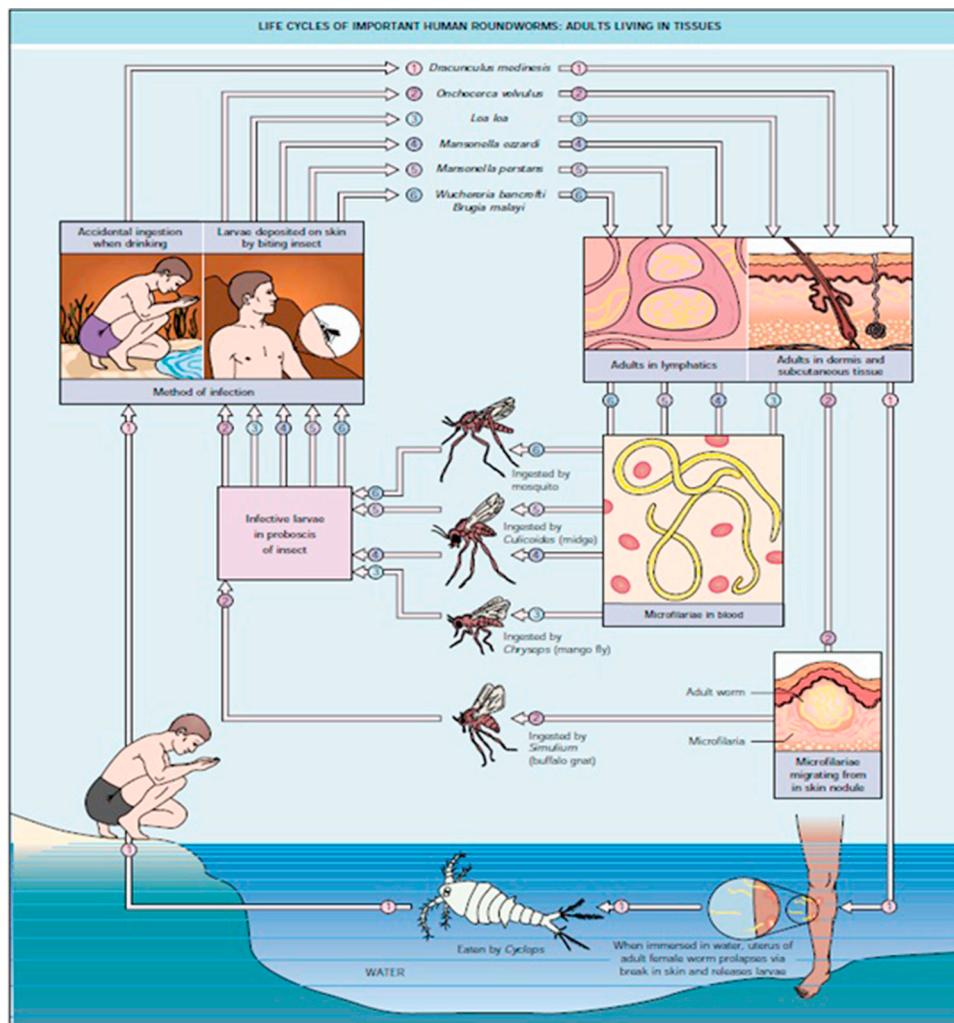


Fig 4. Lifecycle of onchocerciasis, filariasis, *Loa loa*, and Streptocerciasis. Used with permission from Cross JH. Helminths. In: Armstrong D, Cohen J, editors. Infectious diseases. London: Mosby; 1999.

the animal's feces. The larvae continue their life cycle in sand or soil. The mature filariform larvae then infiltrate humans via exposed skin surfaces to begin their new subcutaneous journey.⁸ However, in humans, the larvae are sequestered in the dermis and cannot penetrate further to complete their life cycle because of their lack of specific collagenases. Humans are the end hosts.

Presentation

CLM is characterized by pruritic, erythematous papules or a linear or serpiginous elevated mobile track. The hookworm migrates through the skin at about 1 mm to 3 cm per day (Fig 2). The most commonly affected areas are the feet, buttocks, thighs, and lower legs, but lesions can appear anywhere (Fig 3).⁹ Intense itching usually begins within a few minutes to a few days after filariform

larvae penetration. Symptoms are self-limited and resolve after the nematode dies (approximately 2-8 weeks). Complications of CLM include impetiginization caused by scratching, excoriations, vesiculobullous lesions,¹⁰ and, rarely, folliculitis or erythema multiforme.

Diagnosis

CLM is diagnosed clinically based on history and physical examination. Patients will usually report recent exposure to contaminated sand or soil. The laboratory workup will occasionally reveal eosinophilia or increased immunoglobulin E levels. Obtaining a biopsy specimen is rarely helpful and infrequently reveals larvae given that they have usually migrated away from the site of entry at the time of sampling.

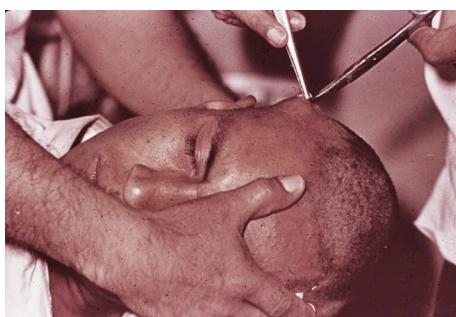


Fig 5. Surgical removal of an onchocercoma. Courtesy of the American Society of Tropical Medicine and Hygiene.

ONCHOCERCIASIS

Key points

- Onchocerciasis is a common tropical disease with dermatologic, ocular, and systemic manifestations
- There are many cutaneous manifestations of the disease, including onchocercoma, which is a palpable onchocercal nodule most commonly found at bony prominences
- The disease is also known as “river blindness” because it is the second most common cause of blindness caused by infection
- Ivermectin and doxycycline are used to treat the disease

Onchocerciasis, also known as river blindness, is a parasitic infectious disease caused by the filarial nematode *Onchocerca volvulus*. The disease is transmitted by the bite of a female black fly (Fig 4) and affects >27 million people, with most cases in sub-Saharan Africa¹¹—although there have been imported cases reported in the United States.¹² The disease has many cutaneous manifestations, including severe pruritus, eczematous dermatitis, lichenification, and subcutaneous and dermal atrophy.

Life cycle

The cycle begins when a black fly ingests microfilariae (MF) of *O. volvulus* from the skin of an infected human host. Within the fly, the MF pass through 2 molts to an infective stage (L3) over a period of 1 to 3 weeks, and at the next blood meal the fly deposits the larvae within the skin of a new human host. The larvae remain in the dermis and subcutaneous tissue, where they undergo 2 additional molts to mature into hair-like adult worms. After maturation, the female adults, now 30 to 80 cm in length, become encapsulated in deep subcutaneous nodules. Once fertilized, the adult females release MF, which can move from the nodules into both subcutaneous tissues and the eyes of the host.



Fig 6. A 14-year-old boy with localized lichenified onchoceriasis on the right lower extremity. Courtesy of the American Society of Tropical Medicine and Hygiene.

Presentation

Onchocercoma is the most distinct cutaneous manifestation of the disease. Onchocercoma is a firm, painless, freely mobile subcutaneous nodule that is often located over a bony prominence. A lesion is typically 1 to 3 cm in diameter (Fig 5). The disease also encompasses many other cutaneous manifestations (Fig 6), and a classification system was developed by Murdoch et al¹³ in 1993 (Table I).

In conjunction with these 5 main categories of disease (acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis, atrophy, and depigmentation), lymphedema of the lower extremities and even elephantiasis may occur in areas of Africa where onchoceriasis is endemic. The groin region may become swollen, with enlarged lymph nodes. “Hanging groin”—a merging of enlarged lymph nodes enclosed by a segment of atrophic and stretched abdominal skin—may also be a feature of chronic onchoceriasis (Fig 7).

Diagnosis

One of the first signs of the infection is severe eosinophilia (up to 40%). The criterion standard of diagnosis is microscopic examination of MF that emerge from bloodless skin snips (Fig 8).¹⁴ A skin snip is a specialized way of obtaining a biopsy specimen. After an area of skin is wiped with alcohol, it is elevated with the tip of a needle and a small segment of the tented skin is shaved off with a razor blade or scalpel. This piece of skin is placed on a slide under a cover slip and immersed in isotonic saline. After 15 to 20 minutes, the preparation is examined for the presence of motile MF that emerge from the tissue.

The diagnosis may also be made through the microscopic examination of subcutaneous nodules

Table I. Cutaneous manifestations of onchocerciasis

Classification	Dermatologic description	Location
Acute papular onchodermititis	Small, 1-3 mm in diameter, pruritic papules that may progress into vesicles or pustules; may be associated with erythema and edema (Fig 6)	Extremities and trunk
Chronic papular onchodermititis	Flat-topped, hyperpigmented, pruritic papules typically 3-9 mm in diameter	Buttocks, waist area, and shoulders
Lichenified onchodermititis	Hyperpigmented, lichenified plaques with associated edema and lymphadenopathy	Extremity (typically limited to 1)
Atrophy	Loss of skin elasticity and excessive wrinkling; may be associated with decreased sweating and hair growth	Buttocks, waist, and upper aspect of the thighs
Depigmentation	Often referred to as "leopard skin"; patches of complete pigment loss are seen except for perifollicular islands of retained normal pigmentation	Anterior shins, less commonly on the abdomen or lateral aspect of the groin

**Fig 7.** A 52-year-old man with hanging groin caused by onchocerciasis. Courtesy of the American Society of Tropical Medicine and Hygiene.**Fig 8.** Microfilariae of *Onchocerca volvulus* from a skin nodule of a patient from Zambia. Courtesy of the Centers for Disease Control and Prevention. (Hematoxylin–eosin stain; original magnification, $\times 1000$.)

that have been removed surgically. The pathology reveals coiled adult female worms on the histologic sections of the nodules. The biopsy results of an involved patch of skin may feature an inflammatory reaction made up of eosinophils, neutrophils and macrophages. At times, the worm may emerge from the skin and mimic *Dracunculus medinensis*.¹⁵

GNATHOSTOMIASIS

Key points

- **The classic diagnostic triad of gnathostomiasis features intermittent migratory swellings/nodules, eosinophilia, and a history of travel to an area of endemicity**
- **The migratory nature of the subcutaneous swellings/nodules help differentiate gnathostomiasis from other causes of subcutaneous nodules**
- **Surgical removal or albendazole are the treatments of choice**

Human gnathostomiasis is a food-borne parasitic zoonotic disease caused by the ingestion of larvae of the genus *Gnathostoma*, seen mostly in tropical and subtropical regions, such as Southeast Asia, Japan, Central and South America, and South Africa.¹⁶ There are increased recent reports of disease in tourists returning from endemic areas. The classic triad of intermittent migratory swellings, eosinophilia, and a history of travel to Southeast Asia or other areas of endemicity should alert physicians to the diagnosis.¹⁷

Life cycle

Humans are accidental hosts in which the parasite fails to reach sexual maturity. The definitive hosts are carnivores, especially fish-eating mammals, where the adult worm (Fig 9) lives coiled up in the wall of the stomach, producing a tumor-like mass. In the definitive hosts, the adult worm, which reaches 13 to



Fig 9. Adult worm seen in gnathostomiasis.



Fig 10. Gnathostomiasis. Note the nodular migratory eosinophilic panniculitis.

55 mm in length, releases eggs into the stomach that are then passed in the feces. Eggs are hatched in freshwater and release first-stage larvae (L1) that mature into third-stage larvae (L3) via 2 intermediate hosts.^{16,18} Humans usually become infected with *Gnathostoma* spp. by eating raw or inadequately cooked freshwater fish or other intermediate hosts, such as snakes, frogs, and chickens.

Presentation

Patients may develop nonspecific symptoms, such as malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric or right upper quadrant pain. These symptoms occur as the larva excysts and migrates through the stomach, intestinal wall, and the liver and may last for 2 to 3 weeks.¹⁹ The worm then migrates to the skin through the subcutaneous tissue, causing the typical migratory swellings and from there may penetrate into deeper tissues.

Cutaneous gnathostomiasis is the most common manifestation of infection. It typically presents with poorly defined, erythematous, edematous, round or oval, pruritic or painful, 5- to 15-cm plaques or indurated, deep-seated nodules that form along the route of larval migration.²⁰ These edematous

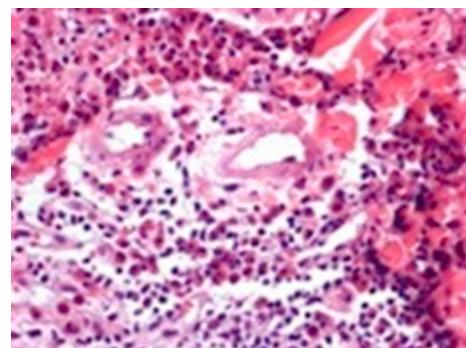


Fig 11. Gnathostomiasis. Note the dense eosinophil infiltration; there was no parasite found in this specimen.



Fig 12. Lymphedema of the left lower extremity caused by lymphatic filariasis.

swellings are intermittent (nodular migratory panniculitis), usually affecting the trunk or upper limbs (Fig 10). They usually occur within 4 weeks of ingestion of the larvae and last for up to 2 weeks. As the larva migrates, subcutaneous hemorrhages may be seen along its tracks, which are pathognomonic of gnathostomiasis and can help differentiate it from other causes of larva migrans (eg, sparganosis or strongyloidiasis).

Episodes of swelling slowly become less intense and shorter in duration, but in untreated patients symptoms may recur intermittently for up to 10 to 12 years. Other less common manifestations of cutaneous gnathostomiasis include skin abscesses or nodules that tend to occur when the larva is migrating more superficially.

Diagnosis

The diagnosis of gnathostomiasis is most commonly made with after a biopsy specimen of the skin is obtained. Expected histologic findings include a dense perivascular and interstitial eosinophilic infiltrate occupying mainly the subcutaneous fat and the dermis (Fig 11).²¹ Flame figures, reminiscent of eosinophilic cellulitis, can be present around collagen bundles in the dermis. It is extremely difficult to find the worm on histologic examination

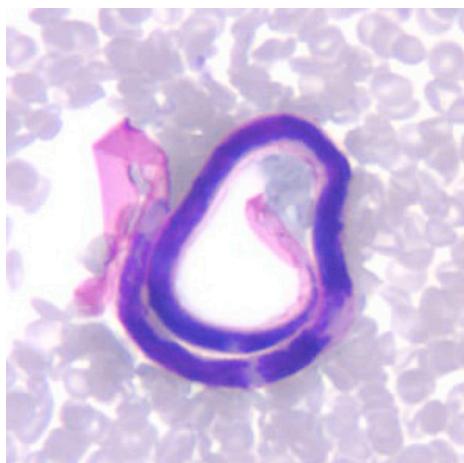


Fig 13. Peripheral blood smear showing microfilaria of *Brugia malayi*. Courtesy of the Centers for Disease Control and Prevention. (Giemsa stain.)



Fig 14. Marked swelling and disfigurement of the right foot caused by podoconiosis. There are multiple firm nodules and hyperkeratotic papillomas.

because the area of infiltration encompasses several centimeters, while the larva measures 2.5 to 12.5 mm long and 0.4 to 1.2 mm wide.²⁰

FILARIASIS

Key points

- Filariasis is caused by the nematodes *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*
- Filariasis presents with lymphedema, primarily in the lower extremity
- Chronic inflammation leads to nonpitting edema and hardening of the tissues, resulting in hyperkeratosis and hyperpigmentation of the skin; fissuring of the skin follows
- Lymphedema is initially reversible; however, persistent infection and compromise to the lymphatic system leads to elephantiasis

Life cycle

Filariasis, or elephantiasis, is a tropical disease characterized by thickening of the skin and



Fig 15. Surgical removal of an adult *Loa loa* worm. Courtesy of Curt Samlaska, MD.

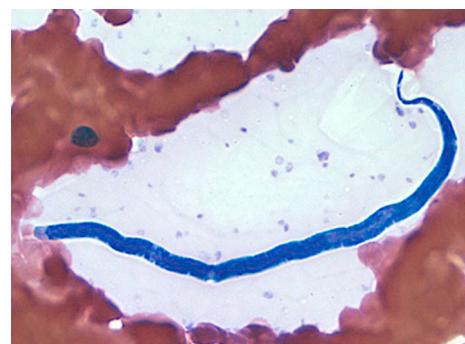


Fig 16. Microfilaria of *Loa loa* in a peripheral blood smear. Courtesy of the Centers for Disease Control and Prevention. (Giemsa stain.)

underlying tissues, especially in the legs and male genitals.²² There are 3 types of nematodes that cause this disease: *Wuchereria bancrofti*, which causes 90% of cases; *Brugia malayi* and *Brugia timori* cause the remaining 10% of cases, most of which are restricted to south and east Asia. Filariasis affects >120 million people in areas of Asia, Africa, the Pacific Islands, several of the Caribbean Islands, and South America.²³ The disease occurs when infected mosquitoes bite a human and deposit L3 larvae into the skin. The larvae then migrate to the lymphatic system, where they develop into adult worms (Fig 4).

Presentation

Lymphatic filariasis manifests primarily as lymphedema of the extremities, genitalia, and breasts (Fig 12). The skin turns warty and thickens with cracks and folds. The affected areas are swollen, painful, and often have a foul smell.

The most common acute manifestation of lymphatic filariasis is acute adenolymphangitis (ALA). ALA is characterized by episodes of fever attacks, inflamed lymph nodes in the groin and axillae, and localized areas of warmth, swelling, redness, and pain. ALA is thought to occur as an immune-mediated response to dying adult worms. ALA episodes recur several times a year, with the

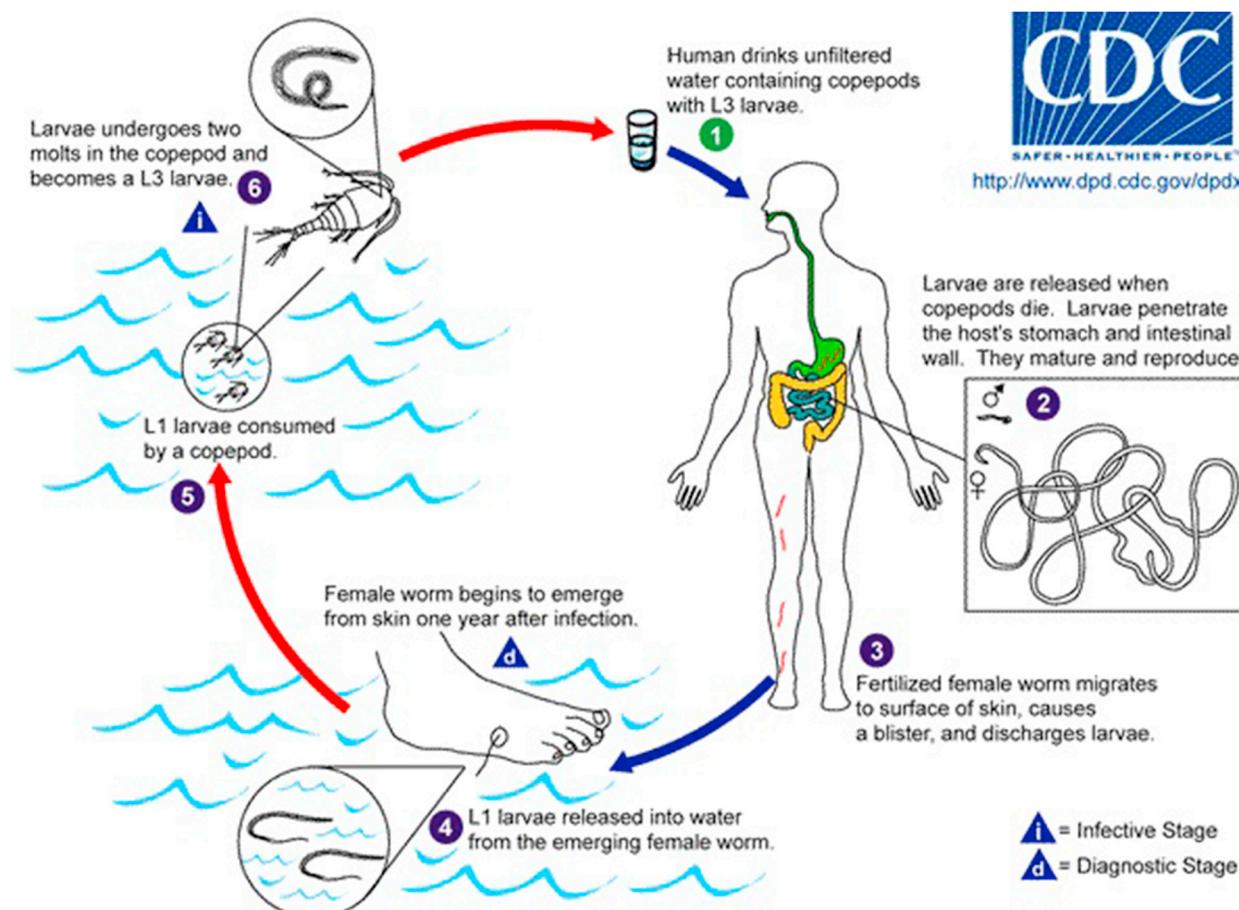


Fig 17. Lifecycle of dracunculiasis. Note that the lesions are intensely painful and patients find relief by having the lesion come in contact with water. Courtesy of the Centers for Disease Control and Prevention.

attacks increasing in frequency and in respect to the degree of lymphedema. This is responsible for elephantiasis of the limbs and the external genitalia. Elephantiasis is a disfiguring, chronic manifestation and presents months to years after initial infection as severe swelling of the extremities, scrotum, vulva, and breasts.²⁴

Another acute manifestation of lymphatic filariasis is acute filarial lymphangitis (AFL), which is rare and presents when adult worms are destroyed in the lymph vessels or lymph nodes either spontaneously or by drug administration. Patients present with small, tender nodules at the site of the dying worms.

Diagnosis

Definitive diagnosis can be made by circulating antigen detection. The most useful antigen detection test is the immunochromatographic test (ICT). This test detects antigens released by adult filarial worms. The test is convenient, mobile, and inexpensive.^{25,26} If circulating antigen testing is not available,

examination of blood smears for MF can be performed. Blood must be taken between 10 PM and 2 AM because of the “nocturnal periodicity” of the filaria. MF can be detected in peripheral blood during the early stages of filariasis, even before clinical manifestations develop (Fig 13). This highly reliable method was the diagnostic standard for many years and is still used in many regions. This test is not useful once lymphedema is present because MF are absent from the blood during this stage.²⁷ Patients will also have high eosinophilia (>10%).

Differential diagnosis

Podoconiosis, also known as “mossy foot,” is a noncommunicable, noninfectious tropical lymphedema and an important differential for filariasis. It is a common cause of lower leg lymphedema in tropical volcanic highland areas (>1000 meters above sea level) with high annual rainfall. It is characterized by below the knee bilateral lower



Fig 18. A Guinea worm extracted from the right lower leg of a Nigerian man. Only a few millimeters are removed each day. The extracted portion of the worm is then wrapped around a small stick or piece of gauze. Courtesy of the Centers for Disease Control and Prevention.



Fig 19. Larva migrans found in the interdigital space between the 4th and 5th digits of the right hand caused by Strongyloidiasis infection. Note that the lesions are more commonly found in the perianal and truncal regions. Courtesy of Penvadee Pattanaprichakul, MD.

limb elephantiasis in barefoot subsistence farmers in farmland areas with red soils derived from alkaline volcanic rock. Although it has only recently been formally designated a “neglected tropical disease” by the World Health Organization,²⁸ it contributes to a significant public health burden in 10 countries across tropical Africa, Northern India, and Central and South America. There has been recent association of variants in human leukocyte antigen class II loci with the disease, suggesting it may be a T cell–mediated inflammatory disease.²⁹

In podoconiosis, persistent lymphedema (Fig 14) is typically below the knee and not associated with scrotal involvement or hydrocoele. Skin changes include the so-called “mossy” hyperkeratosis and series of hard bands or nodules interspersed with deep cracks, folds, and fissures in the skin that harbor mixed infections leading to a strikingly offensive odor in affected individuals.

There are no diagnostic tests for podoconiosis. Exclusion of LF and other causes of lower limb



Fig 20. Disseminated Strongyloidiasis. Note the retiform purpura caused by vessel occlusion and dermal invasion of the larvae.

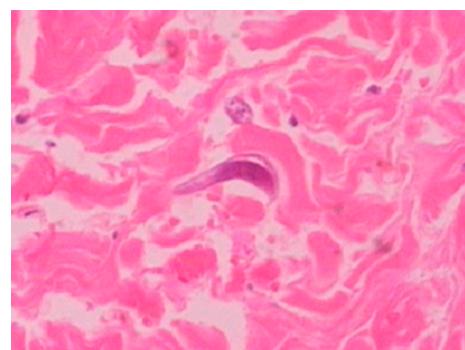


Fig 21. *Strongyloides stercoralis* larvae among the reticular dermis and capillaries. There is no inflammatory reaction.

lymphedema should be excluded before settling on the diagnosis. Treatment is challenging, but simple interventions can lead to substantial improvements in both objective measurements of lymphedema and significant improvement in quality of life.³⁰ Measures include daily washing of the feet and wearing of socks and shoes to prevent contact with the irritant soil responsible for the disease. Debulking surgery has shown to only provide short-term benefit, with subsequent return of lymphedema.

LOIASIS

Key points

- Loiasis, also known as African eye worm, is caused by the filarial nematode *Loa loa*; the vector is a deerfly from the genus *Chrysops*
- The manifestations of disease include transient localized subcutaneous swellings (known as Calabar swellings), which have been reported in approximately 50% of patients
- Migration of the adult worm across the conjunctiva of the eye occurs in approximately 70% of patients
- The treatments of choice are diethylcarbamazine and albendazole



Fig 22. Extraction of *Ascaris lumbricoides*.

Life cycle

Loa loa, also known as African eye worm, is found in West and Central Africa. It is estimated that 3 to 13 million people were infected in 2010.³¹ The 2 main signs of disease are localized subcutaneous swellings and migration of the worm across the conjunctiva. The vector of the disease is a deerfly from the genus Chrysops, which transmits the parasite when it bites a human, most commonly during the rainy season (Fig 4).

Presentation

Most infected people are asymptomatic, especially when they live in endemic areas. Travelers experience symptoms more commonly. Patients present with subcutaneous swellings on the limbs, known as Calabar swellings, which are localized, elastic, cold, transient, painless, pruritic, and migratory.³¹ They are often found near the joints.

The disease can also present as recurrent migratory focal angioedema caused by adult filariae. A raised outline of the skin is occasionally visible, showing the underlying mature filariae. It may involve the limbs and large joints and may present with pain and pruritus. The periorbital area is often affected and the MF may also be seen in the conjunctiva (eye worm disease; Fig 15).

Diagnosis

Loiasis should be considered in patients with a history of travel to an endemic area who present with unexplained peripheral eosinophilia, ocular symptoms, and/or Calabar swellings. The standard diagnostic test is the demonstration of MF on a daytime, Giemsa-stained blood smear (Fig 16) or demonstration of an adult worm removed from subcutaneous or conjunctival tissue. Polymerase chain reaction testing for loiasis is approved in the United States.³²

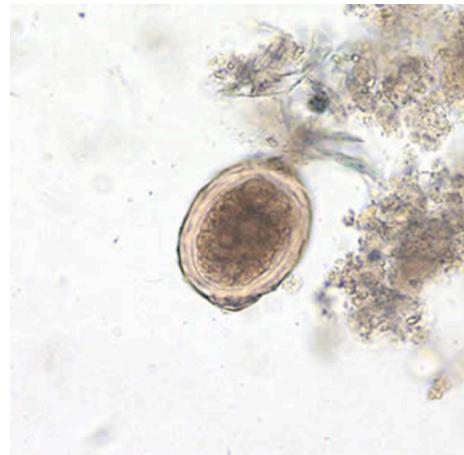


Fig 23. Fertilized egg of *Ascaris lumbricoides* in an unstained wet mount. Courtesy of the Centers for Disease Control and Prevention. (Original magnification: $\times 200$.)

DRACUNCULIASIS

Key points

- Dracunculiasis is transmitted by drinking stagnant water contaminated with copepods containing infective Guinea worm larvae
- Approximately 1 year after infection, a fertilized female worm migrates to the surface of the skin and induces an extremely painful papular lesion; when the infected patient soaks the lesion in water, the worm releases larvae, relieving the discomfort
- To remove the worm, it is slowly coiled out over the course of a few days to a month with a small rod, match, or stick

Dracunculiasis, also known as Guinea worm disease, is a parasitic infection once common in the tropics that is caused by *Dracunculus medinensis*; in recent years it has been nearly eradicated. In 2013, there were 148 reported cases: 113 in south Sudan, 14 in Chad, 11 in Mali, 7 in Ethiopia, and 3 in Sudan.³³

Life cycle

The life cycle begins with human ingestion of unfiltered water containing copepods (tiny aquatic crustaceans, approximately 2-3 mm long) that serve as intermediate hosts. After human ingestion, the copepods are killed by gastric juices and release larvae that penetrate the host stomach and small intestine, which provides an entryway into the abdominal cavity and retroperitoneal space. Here the larvae mature into adults and copulate. Adult females grow to 60 to 100 cm. All of the male worms die in the human host, but the females migrate to subcutaneous tissue. Here the females mature for approximately a year before epicutaneous migration occurs (Fig 17).

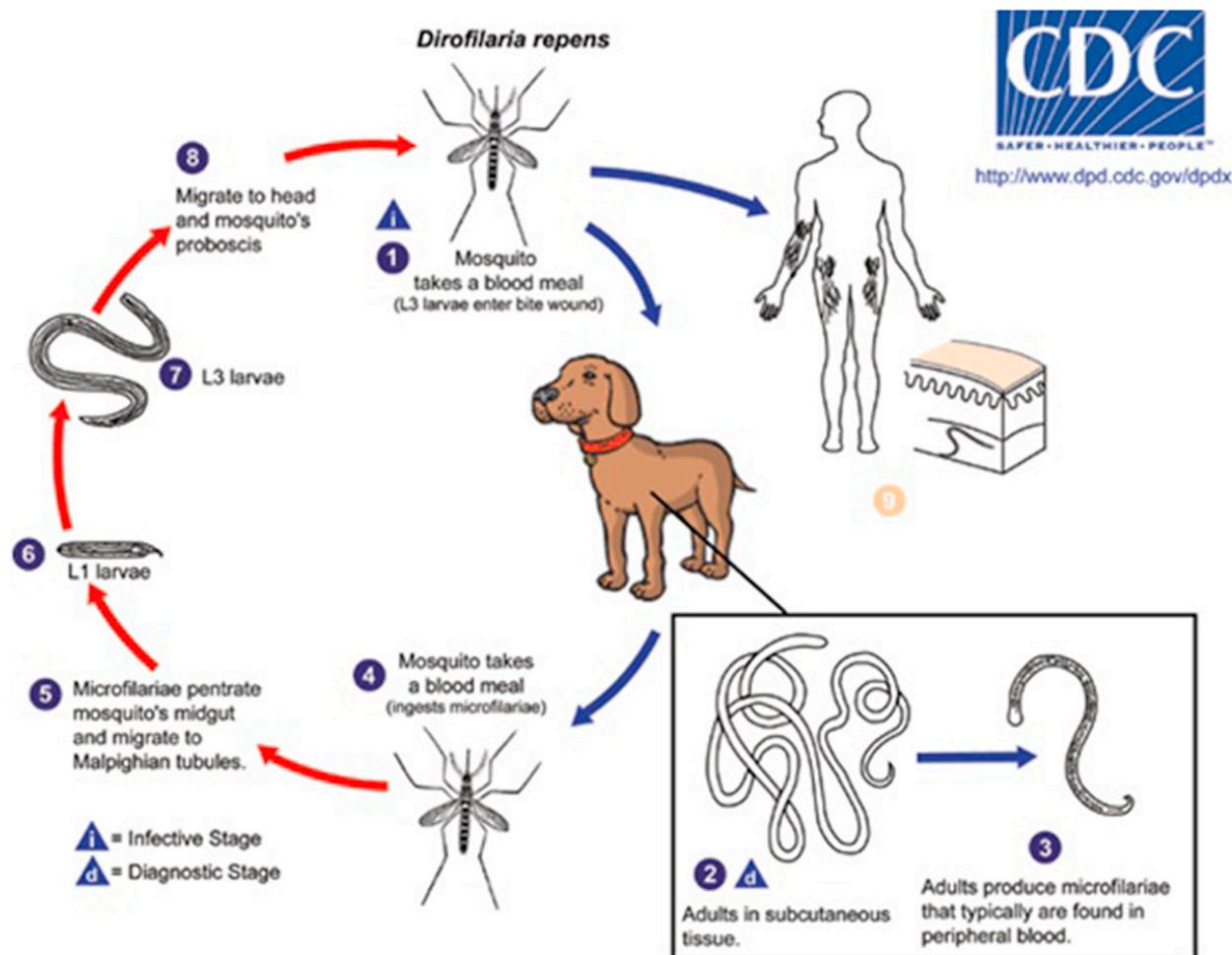


Fig 24. Life cycle of *Dirofilaria repens*. Courtesy of the Centers for Disease Control and Prevention.

Presentation

During subcutaneous migration, patients typically complain of intense pain localized to the path of travel. Patients may also complain of nonspecific symptoms, such as nausea, vomiting, fever, and syncope.

Approximately 1 year after initial ingestion and after epicutaneous migration, urticaria and an erythematous papulonodular lesion are noticed. The lesion is evanescent, being followed by a vesiculobullous lesion with surrounding induration, which causes the patient an intense burning sensation relieved by submerging the lesion in water. There is usually a distinct primary lesion, but a patient may have >20 worms extruding at any given time. Once the lesions are immersed in water, the adult female releases hundreds of thousands of Guinea worm larvae, leaving the water supply contaminated.^{34,35}

If the worm ruptures in the subcutaneous tissue, it causes cellulitis or can heal with calcification. About half of patients have secondary bacterial infections at the site of the vesiculobullous lesion; this is a major cause of morbidity.³⁴

Diagnosis

Diagnosis is made by clinical observation of a worm extruding from a skin lesion (Fig 18) or from a suspected ulcer with a wet smear revealing motile larvae on microscopic examination. Patients usually have eosinophilia with an increased erythrocyte sedimentation rate.

STRONGYLOIDIASIS

Key points

- Strongyloidiasis is typically a gastrointestinal disorder; however, larvae may emerge to the patient's perirectal skin to produce a

Table II. Other nematode infections⁴³⁻⁵⁴

Infection	Epidemiology and transmission	Presentation	Diagnosis
Ascariasis (Fig 22)	Most common helminthic infection worldwide; estimated prevalence rate in the US is 2%; infection in humans occurs with ingestion of water or food contaminated with fertilized Ascaris ova	Urticaria (most common); dermatographism; cutaneous manifestations are typically associated with the pulmonary disease termed Loeffler syndrome or Ascaris pneumonia; prevalence of dermatologic manifestations is approximately 20-25%	Eosinophilia; stool examination reveals characteristic trilayered ova (Fig 23)
Streptocerciasis	<i>Mansonia streptocerca</i> is confined to Central and West Africa; the disease is transmitted by biting midges (Culicoides midges; Fig 4)	Usually asymptomatic; most common dermatologic manifestations include pruritus, especially over the thorax and shoulder; lichenification; hypopigmented macules; and lymphadenopathy; does not cause subcutaneous nodules	Identification of MF in the skin; females are on average 27 mm in length; the MF are shorter and thinner than those in <i>Onchocerca volvulus</i> ; the posterior end of the MF may be bent like a shepherd's crook; patients typically have an eosinophilia
Dirofilaria	Humans are infected with dirofilaria larvae (Fig 24) through mosquito bites (usually Aedes or Culex); most common in the Mediterranean, but has been described in many areas, including the US	Subcutaneous nodule, either tender or nontender; occasionally migratory; may be associated with an abscess; commonly found on the eyelids, scrotum, breasts, arms, and legs	Histologic examination; species identification can be made by analysis of the length and morphology of the parasite; patients do not typically exhibit eosinophilia
Trichinosis	Trichinella is found worldwide and is a serious health concern in areas where raw or undercooked meat is consumed; pigs are the most common source of human infection, and raw or undercooked meat is the main mode of transmission; in the US, this is typically from consumption of home-prepared sausage	Myalgia is the most common complaint (~90% of cases); fever and weakness are also commonly reported; periorbital edema is the most common dermatologic manifestation; occasionally, a nonpruritic urticarial and morbilliform exanthem appears during the parenteral phase in week 3 of infection; the clinical triad of fever, myalgia, and periorbital swelling should alert the dermatologist to the disease; migration to the distal extremities may result in subungual splinter hemorrhages	Eosinophilia; increased creatine phosphokinase; screening ELISA test detects anti-Trichinella IgG; confirmatory test: indirect immunofluorescence

ELISA, Enzyme-linked immunosorbent assay; IgG, immunoglobulin G; MF, microfilariae.

- **distinctive cutaneous eruption termed “larva currens”**
- **Larva currens is characterized by a serpiginous, raised, erythematous track that migrates at 5 to 15 cm per hour, much faster than the creeping eruption of cutaneous larval migrants**

- **Hyperinfection with *Strongyloides* can cause a rapidly progressive and diffuse petechial “thumbprint purpura” eruption that is fatal if untreated**
- **Ivermectin is the treatment of choice**

Strongyloidiasis is caused by the human parasite *Strongyloides stercoralis*. Strongyloidiasis is

Table III. Treatment of nematode infections⁵⁵⁻⁵⁹

Disease	Treatment*	Dosing	Comment
Cutaneous larva migrans	Ivermectin [†]	0.15-0.2 mg/kg QD PO × 1 or 2 days	The disease is essentially self-limited, with antihelminthic therapy relieving symptoms and preventing secondary bacterial infection
Onchocerciasis	Ivermectin	0.15-0.2 mg/kg PO × 1 dose; may repeat in 3-12 months for the life of an adult worm	Ivermectin reduces skin microfilarial worms, but it does not eradicate infection. ⁵⁵
	Doxycycline	100 mg QD PO × 6 wks	Doxycycline kills <i>Wolbachia</i> sp., a bacterium necessary for the nematode to reproduce ⁵⁶
Surgical removal (nodulectomy)			
Gnathostomiasis	Albendazole	400-800 mg PO QD × 21 days ⁵⁷	
	Ivermectin (for pediatric patients)	0.2 mg/kg PO × 2 doses taken 48 hrs apart	
Filariasis	Surgical removal		
	DEC	200 mg PO q12h × 12 days, repeat 10 days later, or 6 mg/kg/day PO × 12 days (pediatric dose), repeat 10 days later	DEC is no longer approved by the FDA, but physicians can obtain the medication from the CDC after the diagnosis has been confirmed; this therapy should be avoided in patients with concurrent onchocerciasis, as it can worsen eye disease; DEC should also be avoided in patients with loiasis because encephalopathy or death may ensue. Patients with lymphedema or elephantiasis will not likely benefit from DEC because most of these patients are not actively infected with the parasite. ⁵⁸
Loiasis	Doxycycline	200 mg QD PO × 6-8 wks	Doxycycline kills <i>Wolbachia</i> sp., a bacterium necessary for the nematode to reproduce
	Ivermectin	0.15-0.2 mg/kg PO × 1 dose	Treatment of choice for patients with concurrent onchocerciasis
	DEC	200 mg QD PO × 21 days	
Dracunculiasis	Albendazole	200 mg BID PO × 21 days	
	Surgical removal		Effective if there is only a single adult worm
	Thiabenzazole	25-37.5 mg/kg PO BID × 3 days	Pharmacologic therapy can be used to decrease inflammation to aid worm removal, but these therapies are not parasiticidal
Strongyloidiasis Ascariasis Mansonella	Metronidazole	200-400 mg PO TID × 3 days	
	Surgical removal		
	Ivermectin	0.2 mg/kg QD PO × 2 days	
Ivermectin	Albendazole	400 mg PO × 1 dose	
	DEC	6 mg/kg/day PO × 12 days	Before administering DEC, onchocerciasis should be excluded because of the possible exacerbation of ocular disease in these patients
Ivermectin			Reduces microfilarial load, but efficacy is unknown ⁵⁹
		0.15 mg/kg × 1	

Continued

Table III. Cont'd

Disease	Treatment*	Dosing	Comment
Dirofilaria	Surgical removal		Often the lesions calcify without any treatment
Trichinosis	Albendazole	5 mg/kg/day × 7 days	Used in conjunction with antihelmintics to help control inflammatory response
	Mebendazole	5 mg/kg/day × 8 to 14 days	
	Thiabendazole	25 mg/kg/day for 8 to 14 days	
	Prednisone	30-60 mg QD PO × 10-14 days	

BID, Twice daily; CDC, Centers for Disease Control and Prevention; DEC, diethylcarbamazine; FDA, US Food and Drug Administration; PO, per os; QD, once daily; TID, three times daily.

*The preferred treatment is listed first.

†Ivermectin safety in children <15 kg is not known and the drug is not recommended for pregnant or lactating females.

a worldwide disease most commonly found in tropical and subtropical regions that causes mild symptoms in immunocompetent individuals but severe and life-threatening symptoms to immunocompromised individuals.

Life cycle

The life cycle begins with direct contact with free-living filariform larvae, usually through contaminated soil. The larvae penetrate the skin on contact and migrate through the body, eventually reaching the small intestine where they mature into adult nematodes and lay their eggs. Noninfective larvae hatch from the eggs and are then either excreted in stool or remain in the intestinal tract to develop into the infective filariform larvae, which migrate towards the perianal opening. There they penetrate the skin and rapidly extend outward, causing cutaneous manifestations.

Unique among helminthic parasites, *S stercoralis* is able to complete its life cycle inside of the human host. Autoinfection occurs when the filariform larvae enter the circulatory system, are carried into the lungs, and are then swallowed into the intestinal tract, repeating the cycle.³⁶

Presentation

Most patients with strongyloidiasis are asymptomatic or do not experience major symptoms. Acute infection is generally characterized by gastrointestinal and pulmonary symptoms. Chronic infection is characterized by dermatologic symptoms. Other patients have eosinophilia that persists for years with the absence of any symptoms. As the larvae migrate out of the intestinal tract, they may reach the perianal skin and move outward. Here they cause a classic urticarial eruption that is centered perianally and extends to the buttocks, thighs, and abdomen in a linear or serpiginous pattern. The rash is thought to be an allergic response to the migrating larvae. Specific to

strongyloidiasis is the rate at which the rash extends, noted to be from 5 to 15 cm per hour and gives rise to the name "larva currens" (Fig 19). This rash may last a few hours to days, but autoinfection cycles can cause the rash to recur for weeks to years.

In immunocompromised individuals, hyperinfection with *Strongyloides* can cause a rapidly progressive and diffuse petechial "thumbprint purpura" eruption, characteristically radiating from the periumbilical area (Fig 20).³⁷⁻⁴⁰ These skin manifestations are thought to be attributed to dermal invasion of a large number of larvae that migrate through the vessel walls.⁴¹ Hyperinfection is usually present with other systemic involvement, such as sepsis or septic shock, and signifies a poor prognosis with high rates of fatality.

Diagnosis

The criterion standard for diagnosis of strongyloidiasis is microscopic stool examination to visualize the larvae. The serum immunoglobulin E level is usually elevated, in line with other migrating helminth infections. Enzyme-linked immunosorbent assay for specific anti-*Strongyloides* immunoglobulin G antibodies is sometimes used as a screening assay.⁴² On histologic examination, the filariform larvae may be seen (Fig 21).

CONCLUSION

Other nematode infections with cutaneous manifestations include ascariasis, streptocerciasis, dirofilaria, and trichinosis (Figs 22 to 24 and Table II). In conclusion—and considering that there is no vaccine available to prevent nematode infections—the most effective management is treatment (Table III) and prevention. Dracunculiasis is the second (after smallpox) human infectious disease scheduled for eradication and the first infectious disease to be eradicated without the use of a vaccine. Prevention of other nematode

infections depends on the epidemiology: controlling arthropod vectors for onchocerciasis, filariasis, streptocerciasis, dirofilariasis and loiasis; cooking food thoroughly for gnathostomiasis and trichinosis, wearing shoes to prevent cutaneous larval migrans and strongyloidiasis, and providing clean drinking water for ascariasis. Therefore, most improvements in sanitary conditions and public health will lead to reductions in nematode infections.

REFERENCES

1. Hotez PJ. Ten global "hotspots" for the neglected tropical diseases. *PLoS Negl Trop Dis.* 2014;8:e2496.
2. Hotez PJ, Murray KO, Buekens P. The Gulf Coast: a new American underbelly of tropical diseases and poverty. *PLoS Negl Trop Dis.* 2014;8:e2760.
3. Parise ME, Hotez PJ, Slutsker L. Neglected parasitic infections in the United States: needs and opportunities. *Am J Trop Med Hyg.* 2014;90:783-785.
4. Hotez PJ. Fighting neglected tropical diseases in the southern United States. *BMJ.* 2012;345:e6112.
5. Barry MA, Bezdek S, Serpa JA, et al. Neglected infections of poverty in Texas and the rest of the United States: management and treatment options. *Clin Pharmacol Ther.* 2012;92:170-181.
6. Hotez PJ, Bottazzi ME, Dumonteil E, et al. Texas and Mexico: sharing a legacy of poverty and neglected tropical diseases. *PLoS Negl Trop Dis.* 2012;6:e1497.
7. Hotez PJ. America's most distressed areas and their neglected infections: the United States Gulf Coast and the District of Columbia. *PLoS Negl Trop Dis.* 2011;5:e843.
8. Centers for Disease Control and Prevention website. Parasites—Zoonotic hookworm. Available at: <http://www.cdc.gov/parasites/zoonotichookworm/biology.html>. Accessed May 25, 2014.
9. Jelinek T, Maiwald H, Nothdurft HD, Loscher T. Cutaneous larva migrans in travelers: synopsis of histories, symptoms, and treatment of 98 patients. *Clin Infect Dis.* 1994;19:1062-1066.
10. Heukelbach J, Feldmeier H. Epidemiological and clinical characteristics of hookworm-related cutaneous larva migrans. *Lancet Infect Dis.* 2008;8:302-309.
11. Basanez MG, Pion SD, Churcher TS, et al. River blindness: a success story under threat? *PLoS Med* 2006;3:e371.
12. Okulicz JF, Stibich AS, Elston DM, Schwartz RA. Cutaneous onchocercoma. *Int J Dermatol.* 2004;41:170-172.
13. Murdoch ME, Hay RJ, Mackenzie CD, et al. A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol.* 1993;129:260-269.
14. Enk CD. Onchocerciasis—river blindness. *Clin Dermatol.* 2006;24:176-180.
15. Eberhard ML, Ruiz-Tiben E, Korkor AS, et al. Emergence of *Onchocerca volvulus* from skin mimicking *Dracunculus medinensis*. *Am J Trop Med Hyg.* 2010;83:1348-1351.
16. Rusnak JM, Lucey DR. Clinical gnathostomiasis: case report and review of the English-language literature. *Clin Infect Dis.* 1993;16:33-50.
17. Herman JS, Chiodini PL. Gnathostomiasis, another emerging imported disease. *Clin Microbiol Rev.* 2009;22:484-492.
18. Yoshimura K. Chapter 34. In: Collier L, Balows A, Sussman M, eds. *Topley and Wilson's microbiology and microbial infections.* 9th ed. London, United Kingdom: Hodder Education; 1998: 651-659.
19. Guitierrez Y. *Diagnostic pathology of parasitic infections with clinical correlations.* 2nd ed. Oxford, United Kingdom: Oxford University Press; 2000.
20. Bravo F, Sanchez MR. New and re-emerging cutaneous infectious diseases in Latin America and other geographic areas. *Dermatol Clin.* 2003;21:655-668. viii.
21. Jarell AD, Dans MJ, Elston DM, et al. Gnathostomiasis in a patient who frequently consumes sushi. *Am J Dermatopathol.* 2011;33:e91-e93.
22. Mendoza N, Li A, Tyring S. Filariasis: diagnosis and treatment. *Dermatol Ther.* 2009;22:475-490.
23. Meeting of the International Task Force for Disease Eradication. *Wkly Epidemiol Rec.* 2009;84:89-94.
24. Shenoy RK, Kumaraswami V, Suma TK, et al. A double-blind, placebo-controlled study of the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis. *Ann Trop Med Parasitol.* 1999;93:367-377.
25. Centers for Disease Control and Prevention website. Filariasis. Available at: <http://www.cdc.gov/parasites/lymphaticfilariasis/>. Accessed May 14, 2014.
26. Chandrasena TG, Premaratna R, Abeyewickrema W, de Silva NR. Evaluation of the ICT whole-blood antigen card test to detect infection due to *Wuchereria bancrofti* in Sri Lanka. *Trans R Soc Trop Med Hyg.* 2002;96:60-63.
27. Pfarr KM, Debrah AY, Specht S, Hoerauf A. Filariasis and lymphoedema. *Parasite Immunol.* 2009;31:664-672.
28. World Health Organization website. Podoconiosis: endemic nonfilarial elephantiasis. Available at: http://www.who.int/neglected_diseases/diseases/podoconiosis/en/. Accessed May 6, 2014.
29. Tekola Ayele F, Adeyemo A, Finan C, et al. HLA class II locus and susceptibility to podoconiosis. *N Engl J Med.* 2012;366:1200-1208.
30. Sikorski C, Ashine M, Zeleke Z, Davey G. Effectiveness of a simple lymphedema treatment regimen in podoconiosis management in southern Ethiopia: one year follow-up. *PLoS Negl Trop Dis.* 2010;4:e902.
31. Klion A, Nutman T. Loiasis and mansonella infections. In: Guerrant R, Walker D, Weller P, eds. *Tropical infectious diseases: principles, pathogens, and practice.* New York: Elsevier; 2011.
32. Fink DL, Kamgnio J, Nutman TB. Rapid molecular assays for specific detection and quantitation of *Loa loa* microfilaria. *PLoS Negl Trop Dis.* 2011;5:e1299.
33. The Carter Center website. Guinea worm eradication program. Available at: http://www.cartercenter.org/health/guinea_worm/index.html. Accessed April 30, 2014.
34. Adeyeba OA. Secondary infections in dracunculiasis: bacteria and morbidity. *Int J Zoonoses.* 1985;12:147-149.
35. Assimwe FT, Hengge U. Other helminths: dracunculiasis. In: Lupi O, Tyring S, Hengge U, eds. *Tropical dermatology.* New York: Elsevier; 2006:71-73.
36. Centers for Disease Control and Prevention website. Parasites—strongyloides. Available at: <http://www.cdc.gov/parasites/strongyloides/index.html>. Accessed April 2, 2014.
37. Vitiello M, Shelling M, Camacho I, et al. Fatal cutaneous Strongyloidiasis as a side effect of pemphigus foliaceus treatment with mycophenolate mofetil. *J Drugs Dermatol.* 2011;10:418-421.
38. Martin SJ, Cohen PR, MacFarlane DF, Grossman ME. Cutaneous manifestations of *Strongyloides stercoralis* hyperinfection in an HIV-seropositive patient. *Skinmed.* 2011;9:199-202.

39. Galimberti R, Ponton A, Zaputovich FA, et al. Disseminated strongyloidiasis in immunocompromised patients—report of three cases. *Int J Dermatol.* 2009;48:975-978.
40. Purvis RS, Beightler EL, Diven DG, et al. Strongyloides hyperinfection presenting with petechiae and purpura. *Int J Dermatol.* 1992;31:169-171.
41. von Kuster LC, Genta RM. Cutaneous manifestations of strongyloidiasis. *Arch Dermatol.* 1988;124:1826-1830.
42. Carroll MS, Karthigasu KT, Grove DL. Serodiagnosis of human strongyloidiasis by an enzyme-linked immunosorbent assay. *Trans R Soc Trop Med Hyg.* 1981;75:706-709.
43. Tietze PE, Tietze PH. The roundworm, *Ascaris lumbricoides*. *Prim Care.* 1991;18:25-41.
44. Centers for Disease Control and Prevention website. Parasites—ascariasis. Available at: <http://www.cdc.gov/parasites/ascariasis/index.html>. Accessed April 2, 2014.
45. Katsambas A, Dessinioti C. Parasitic diseases of the skin. In: Bope E, Kellerman R, eds. *Conn's current therapy*. Philadelphia (PA): Saunders/Elsevier; 2013.
46. Fischer P, Bamuhiiuga J, Buttner DW. Occurrence and diagnosis of *Mansonella streptocerca* in Uganda. *Acta Trop.* 1997;63:43-55.
47. Jelinek T, Schulte-Hillen J, Löscher T. Human dirofilariasis. *Int J Dermatol.* 1996;35:872.
48. Warthan ML, Warthan TL, Hearne RH, et al. Human dirofilariasis: raccoon heartworm causing a leg nodule. *Cutis.* 2007;80:125-128.
49. Khoramnia R, Wegner A. Images in clinical medicine: subconjunctival *Dirofilaria repens*. *N Engl J Med.* 2010;363:e37.
50. Fuentes I, Cascales A, Ros JM, et al. Human subcutaneous dirofilariasis caused by *Dirofilaria repens* in Ibiza, Spain. *Am J Trop Med Hyg.* 1994;51:401-404.
51. Gottstein B, Pozio E, Nockler K. Epidemiology, diagnosis, treatment, and control of trichinellosis. *Clin Microbiol Rev.* 2009;22:127-145.
52. Chaudhry AZ, Longworth DL. Cutaneous manifestations of intestinal helminthic infections. *Dermatol Clin.* 1989;7:275-290.
53. Nelson S, Warschaw K. Protozoa and worms. Chapter 83. In: Bolognia J, Jorizzo J, Schaffer J, et al, eds. *Dermatology*. 3rd ed. New York: Elsevier; 2012:1391-1421.
54. Moskwa B, Bien J, Cabaj W, et al. The comparison of different ELISA procedures in detecting anti-*Trichinella* IgG in human infections. *Vet Parasitol.* 2009;159:312-315.
55. Duke BO. Evidence for macrofilaricidal activity of ivermectin against female *Onchocerca volvulus*: further analysis of a clinical trial in the Republic of Cameroon indicating two distinct killing mechanisms. *Parasitology.* 2005;130(part 4):447-453.
56. Hoerauf A, Specht S, Buttner M, et al. Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. *Med Microbiol Immunol.* 2008;197:295-311.
57. Kraivichian P, Kulkumthorn M, Yingyourd P, et al. Albendazole for the treatment of human gnathostomiasis. *Trans R Soc Trop Med Hyg.* 1992;86:418-421.
58. Centers for Disease Control and Prevention website. Parasites—lymphatic filariasis. Available at: <http://www.cdc.gov/parasites/lymphaticfilariasis/treatment.html>. Accessed May 25, 2014.
59. Fischer P, Tukesiga E, Buttner DW. Long-term suppression of *Mansonella streptocerca* microfilariae after treatment with ivermectin. *J Infect Dis.* 1999;180:1403-1405.

Mucocutaneous manifestations of helminth infections

Trematodes and cestodes

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Learning objectives

After completing this learning activity, participants should be able to describe the cutaneous manifestations of infections by trematodes and cestodes and identify appropriate therapy.

Disclosures

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In the 21st century, despite increased international travel for vacation, work, and medical missions and immigration into the United States, there is little published in the dermatology literature regarding the cutaneous manifestations of helminth infections. It has been estimated that 20% to 70% of international travelers suffer from some travel-related health problem. Approximately 17% of travelers seek medical care because of cutaneous disorders, many related to infectious etiologies. This review will focus on cutaneous diseases caused by helminth infections. Part I of the review focused on nematode infections; part II will focus on trematode and cestode infections. Nematodes are roundworms that cause diseases with cutaneous manifestations, such as cutaneous larval migrans, onchocerciasis, filariasis, gnathostomiasis, loiasis, dracunculiasis, strongyloidiasis, ascariasis, streptocerciasis, dirofilariasis, and trichinosis. Trematodes, also known as flukes, cause schistosomiasis, paragonimiasis, and fascioliasis. Cestodes (tapeworms) are flat, hermaphroditic parasites that cause diseases such as sparganosis, cysticercosis, and echinococcus. (J Am Acad Dermatol 2015;73:947-57.)

Key words: cysticercosis; echinococcus; fascioliasis; helminth; paragonimiasis; parasite; schistosomiasis; travel.

TREMATODE INFECTIONS

Key points

- Trematode infections are important causes of morbidity and mortality worldwide
- Several trematode infections have distinguishing dermatologic signs with which dermatologists should be familiar

- Praziquantel is the drug of choice for all trematode infections except fascioliasis, for which triclabendazole is the drug of choice

Trematodes, also known as flukes, cause infection worldwide. Trematodes have complex life cycles that involve snails as intermediate hosts. Most

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Table I. Treatment of trematode and cestode infections

Disease	Treatment	Dosage	Comment
Schistosomiasis			
Cercarial dermatitis	Symptomatic therapy	Triamcinolone topical cream Hydroxyzine	0.5% cream apply to affected area BID ×1 week 25 mg PO Q6H PRN for pruritus ×1 week
Acute schistosomiasis syndrome (Katayama fever) ¹	Praziquantel Prednisolone ²		20 mg/kg PO BID ×3 days 40 mg PO QD ×3 days
Late cutaneous schistosomiasis	Praziquantel		60 mg/kg PO ×2 or ×3 doses at least 3 hours apart
Paragonimiasis	Praziquantel ³	25 mg/kg/day PO divided Q8H ×3 days	Anticonvulsant therapy is warranted in patients with cerebral paragonimiasis
	Thiabendazole	10 mg/kg PO ×1 or ×2 doses	Acceptable second-line therapy for patients who cannot tolerate praziquantel; this drug is only available through the CDC
Fascioliasis	Triclabendazole	10 mg/kg PO QD ×1 or ×2 days	Unlike the majority of fluke infections, fascioliasis has a poor response to praziquantel ³ ; 1 study reported a cure rate of >90% after treatment with triclabendazole ⁴
Sparganosis	Surgical excision		There is usually only 1 tapeworm and it cannot reproduce within the individual; there is no current drug therapy effective against <i>S proliferum</i> —the most effective treatment is to remove the entire larva from the tissues ⁵
Subcutaneous cysticercosis	Surgical excision		All patients with subcutaneous or intramuscular cysticercosis should undergo radiographic imaging to evaluate for neurocysticercosis ⁶
Subcutaneous echinococcosis	Surgical excision		Care during surgery is advised to avoid possible anaphylactic reaction or spillage of protoscoleces ⁷

BID, Twice daily; CDC, Centers for Disease Control and Prevention; PO, per os; PRN, as required; QD, daily.

trematodes are hermaphrodites and are able to self-reproduce. They have emerged as important tropical infections, causing disease in hundreds of millions of individuals globally. Here we review the important mucocutaneous manifestations and treatment (Table I) of trematode infections.

SCHISTOSOMIASIS

Key points

- Schistosomiasis is the most prevalent trematode infection, with >200 million individuals infected
- Infection can cause “swimmer’s itch,” a pruriginous and urticarial erythematous papular

eruption typically found on the lower legs or feet

- Cutaneous disease can be treated with topical triamcinolone; late or advanced cutaneous disease warrants the use of oral praziquantel

Schistosomiasis, also known as bilharziasis in some endemic areas, is considered the second most important tropical disease after malaria in terms of public health importance. The disease is endemic in >60 countries globally—usually in tropical and subtropical regions—and affects >200 million people.⁸ In a global surveillance study conducted

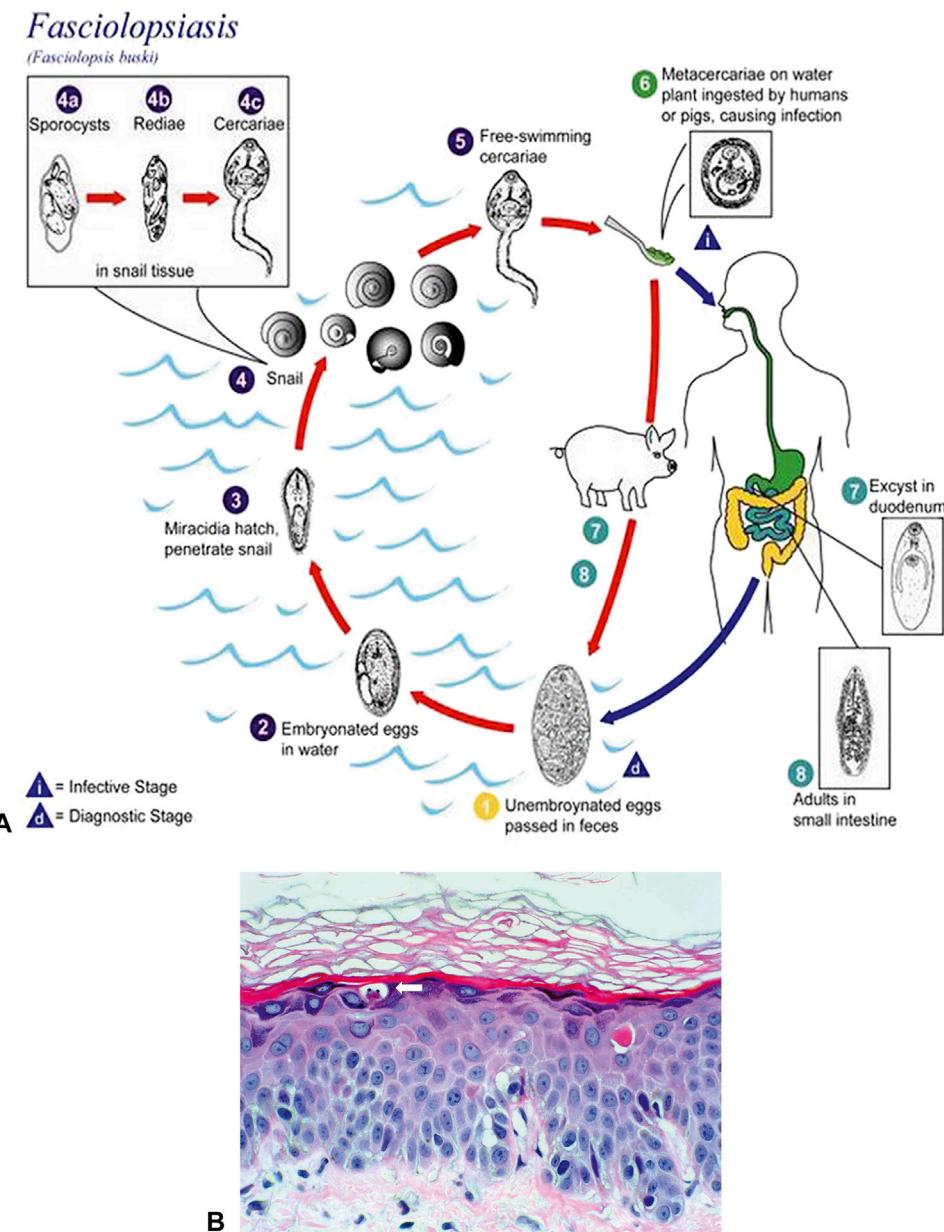


Fig 1. A, Life cycle of Schistosomiasis. B, Cercaria of *Schistosoma mansoni*. Arrow indicates diagnostic features. (A, Courtesy of the Centers for Disease Control and Prevention.)

between 1997 and 2008, 410 cases of schistosomiasis were identified in travelers reporting illnesses. The majority of cases (83%) were obtained in Africa.⁹ Many researchers believe that immunization with an antischistosomiasis vaccine is the best method for disease control. Computational vaccinology is being used to discover potential vaccines.^{10,11}

Life cycle

Humans become infected with schistosomiasis when free-swimming larvae (Cercariae; Fig 1, A) released by freshwater snails are chemically stimulated to directly penetrate the skin upon contact

with aliphatic hydrocarbons, such as the free fatty acids produced on the skin by bacterial esterases. *Schistosoma* sp. enters the epidermal layer of the skin in <30 minutes and arrest when they reach the dermis, which appears to present a temporary barrier to further penetration. They remain at this location for about 40 hours and then penetrate the vascular system, where they mature into adults. Ingestion of water contaminated with cercariae can also transmit the larvae to the intestinal tract. The larvae eventually reach the mesenteric venules (*Schistosoma mansoni* and *Schistosoma japonicum*) or rectovesical plexus (*Schistosoma*



Fig 2. Multiple schistosomal granulomas. (Courtesy of Adel Zaghloul, MD.)



Fig 3. Schistosomal granuloma overlying the left labia minora. (Courtesy of Adel Zaghloul, MD.)

haematobium)—via the external vascular system or through penetration of the intestinal wall—where the females begin laying eggs daily.¹² Host response to the eggs is characterized by a granulomatous reaction at these sites. Eggs are shed in the feces and urine of the host. Upon reaching the outside environment, eggs hatch into larvae, which infect freshwater snails and renew the life cycle. In human infection, adult worms can survive in the host for >30 years by some estimates, but they do not multiply.¹³

Presentation

The disease is acquired by contact with fresh water containing live cercariae (Fig 1, B) and by drinking

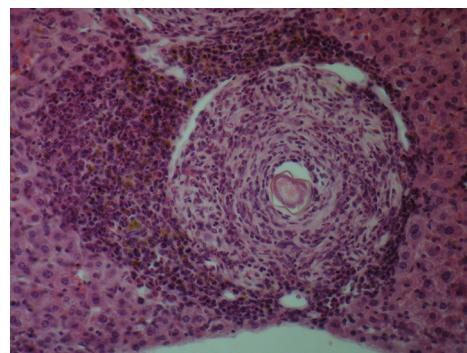


Fig 4. *Schistosoma mansoni* granuloma within the liver.

infested water. Skin manifestations begin within minutes as a nonspecific hypersensitivity reaction to the cercariae penetration. A pruriginous and urticarial erythematous papular eruption can develop within hours of infection in individuals who have been previously sensitized.¹⁴ This eruption, typically found on the lower legs or feet, is termed “swimmer’s itch” and can last for several days. In individuals with previous eruptions, a more rapid severe reaction occurs. Avian and mammalian schistosome species can also cause swimmer’s itch in humans.¹⁵ Humans are accidental targets of these schistosomal species, and the larvae die shortly after initial penetration because humans are not suitable hosts. When the larvae die, a self-limited reaction occurs that is often more intense than that seen from a human schistosome.

Symptoms of acute schistosomiasis, also known as Katayama fever, are normally found in children or young adults. Katayama fever typically occurs 2 to 8 weeks after exposure and results in a systemic hypersensitivity reaction against the migrating parasites. Symptoms are more likely to occur in travelers and other nonimmune hosts. Patients complain of fever, chills, diarrhea, and headache.¹⁶ Other symptoms include urticaria, purpura, and edema of the extremities, genitals, and trunk.

Late skin involvement, bilharziasis cutanea tarda, occurs in persons with chronic, visceral disease. The disease is characterized by papular, granulomatous, or verrucous lesions caused by the deposition of eggs in the dermis (Figs 2 and 3). When lesions are present, they manifest as skin-colored or slightly pigmented 2- to 4-mm oval papules that may form clusters. The lesions are firm on palpation and are associated with pruritus. The lesions appear in crops; without treatment, they will remain unchanged. Lesions in the genital and perineal regions are most common, though there are reports of extraanogenital bilharziasis in the medical literature.¹⁷⁻¹⁹ Some experts have claimed that these lesions may contribute to the HIV endemic in Africa. The sores may serve as an



Fig 5. Adult worm of *Paragonimus westermani*. (Courtesy of the Centers for Disease Control and Prevention.)

entry point for HIV, because the worms and eggs attract CD4 T cells²⁰—however, more research needs to be completed to support this theory.

Diagnosis

Cercarial dermatitis can be presumed from the correct history, epidemiologic setting, and clinical findings. The diagnosis is usually confirmed by microscopic detection of eggs in the urine or feces. In *S japonicum* and *S mansoni*, microscopic evaluation of a biopsy section may provide the diagnosis (Fig 4). An enzyme-linked immunosorbent assay (ELISA) to detect antischistosomal immunoglobulin G (IgG), IgM, and IgE is available and is used to distinguish acute from chronic infection. Laboratory test results generally feature an elevated erythrocyte sedimentation rate,²¹ eosinophilia, and mildly abnormal liver function, principally in patients with acute schistosomiasis.

Histologically, cercarial dermatitis is characterized by spongiosis and a mixed inflammatory infiltrate composed of histiocytes, lymphocytes, neutrophils, and eosinophils. Genital and perineal lesions feature hyperkeratosis and acanthosis and occasionally prominent pseudoepitheliomatous hyperplasia. The dermis may contain numerous ova, which can be associated with a granulomatous reaction. Ectopic extragenital lesions contain ova in the superficial dermis associated with granulomas.

Monoclonal antibodies that detect circulating antigen are quite sensitive and specific for establishing the diagnosis.¹⁸

PARAGONIMIASIS

Key points

- **Paragonimiasis is most commonly caused by the lung fluke *Paragonimus westermani*, which is typically acquired through the consumption of raw or undercooked crustaceans**

- **Skin findings in paragonimiasis usually present as painless migratory subcutaneous nodules, most frequently on the abdominal wall, inguinal region, and proximal lower extremities**
- **Oral praziquantel is the drug of choice for treatment, with concurrent anticonvulsant therapy for individuals with cerebral involvement**

Paragonimiasis (lung fluke) is caused by the consumption of freshwater crustaceans containing living encysted larvae called metacercariae.²² The most common form is the oriental lung fluke, *Paragonimus westermani* (Fig 5). The disease most frequently involves the lungs, but a minority of cases present with migratory subcutaneous nodules. In China, 2 rare species, *Paragonimus szechuanensis* and *Paragonimus hueitungensis*, are most closely associated with subcutaneous disease.

Paragonimiasis primarily occurs in several parts of the Far East. Other less common species have been reported in West Africa and both Central and South America. An estimated 20 million people were infected worldwide in 2013.²³ The prevalence of the disease varies with the cultural eating customs in the region. Most cases are acquired after the consumption of raw or undercooked seafood. The disease can present in travelers returning from endemic areas. In 1 case report, a French tourist visiting Gabon developed cutaneous paragonimiasis after eating undercooked freshwater crabs.²⁴

The disease is rare in the United States; however, there is 1 case series from Missouri noting a total of 9 patients between July 2006 and September 2010 who were infected with the disease after eating raw or undercooked crayfish while camping along and canoeing in Missouri rivers.²⁵

Life cycle

The life cycle of paragonimiasis involves 2 intermediate hosts and a definitive host.²⁶ Eggs are excreted from human sputum or via feces if swallowed. Once in the external environment and without a host, eggs self-embryonate to release miracidiae, which are free-swimming larvae. Miracidiae penetrate into snails, the first intermediate host. In snails, the miracidiae go through several developmental stages—sporocysts to rediae to cercariae—that are produced within the gonads of the snail. Cercariae directly migrate to the snail hindgut and eventually emerge from the rectal tissues. The cercariae then invade the crustacean, the second intermediate host, and encyst to become metacercariae. Humans consume the metacercariae

from raw or undercooked crustaceans. In the human duodenum, the metacerariae excyst. The metacerariae penetrate through the intestinal wall into the peritoneal cavity, then to the abdominal wall, then through the diaphragm into the lungs. They are coughed up or swallowed, and the cycle repeats itself. Adults can produce as many as 20,000 eggs per day.²⁷

Presentation

Cutaneous presentation is rare. Cutaneous manifestations occur before, after, or concurrently with pulmonary manifestations. The disease usually presents as a slowly migratory subcutaneous nodule. The subcutaneous nodule is usually single, though there is at least 1 report in the literature of multifocal lesions.²⁸ The lesions occur most frequently on the abdominal wall, inguinal region, and proximal lower extremities.

The differential diagnosis includes gnathostomiasis, sparganosis, and onchocerciasis, because these also present with migratory subcutaneous nodules. The nodules in paragonimiasis are usually painless, while in the other conditions typically present with pain and pruritus.²⁹

Cerebral paragonimiasis is the most common extrapulmonary site of involvement but is found in <1% of all patients. A feared complication of disease, the parasite can penetrate the meninges, leading to eosinophilic meningitis and encephalitis.³⁰

Diagnosis

The diagnosis is made by visualization of *Paragonimus* ova or adult worm in the excisional biopsy specimen or with a positive serologic test in light of a subcutaneous nodule. Parasites are not often found in biopsy specimens. The diagnosis should be made on clinical grounds in a patient with a migratory subcutaneous nodule with a history of consumption of raw or undercooked crayfish or freshwater crabs.²⁹

In cerebral paragonimiasis, computed tomography or magnetic resonance imaging scans may reveal cystic, ccreng-enhancing lesions with surrounding edema.³¹

FASCIOLIASIS

Key points

- **Fascioliasis is caused by the ingestion of water plants or water contaminated with the liver flukes *Fasciola hepatica* and *Fasciola gigantica***
- **Urticaria is the most common cutaneous presentation, usually found in conjunction with eosinophilia**
- **Fascioliasis responds poorly to praziquantel; triclabendazole is the preferred treatment**

Fascioliasis is caused by the liver flukes *Fasciola hepatica* and *Fasciola gigantica*. The disease has been present among humans for centuries; liver fluke fragments have been found in an Egyptian mummy and mentioned in Renaissance literature from the 17th century.³²

Fasciola is mostly centered in temperate regions with large populations of sheep and cattle, such as Portugal, the Nile delta, Iran, China, and the Andean regions of Peru, Ecuador, and Bolivia. The Nile delta, with its standing or slow-moving temperate waters, contains nearly one-third of all cases globally. An estimated 2.4 million people are infected worldwide, with prevalence increasing since the late 20th century. Incidence in developed countries is very rare and is usually seen in travelers to and immigrants from endemic regions.³³

Life cycle

Adult forms of *Fasciola* can grow up to 30 mm in length and 13 mm in width and live in the intrahepatic bile ducts of the host.³⁴ Eggs are passed down the biliary tree into the intestinal tract, where they are released in feces. If they reach water, the eggs become embryonated and release miracidia, which are free-living, motile, premature larvae. Miracidia find snail hosts and undergo several developmental changes forming sporocysts, rediae, and eventually become cercariae, the motile mature larval form. Cercariae implant onto water plants and encyst to become metacerariae, the infective form of *Fasciola*. Contaminated water plants or water is then ingested by the host, which allows the metacerariae to hatch within the small intestine and release larvae that migrate through the intestinal wall and peritoneal cavity before entering the liver. These larvae then slowly migrate through the liver and eventually rest within the bile ducts, where they mature into adults and lay eggs. Eggs are then passed via the biliary system into the intestinal tract and are released in stool.^{33,34}

Presentation

The most common cutaneous presentation is urticaria during the acute phase of infection.³⁴ While a nonspecific symptom, it is usually found in conjunction with eosinophilia, jaundice, and gastrointestinal symptoms.

Less commonly, *Fasciola* can cause ectopic infections in the skin as the larva migrates to different areas of the body.³⁵ Subcutaneous nodules ≤6 cm in size have been reported in a few cases and represent aberrant superficial larval migration.^{36,37} A Vietnamese case report described a “creeping eruption” caused by *Fasciola* in which the patient

developed a small red vesicle that gradually became a painful serpiginous and vesicular track.³⁸

Diagnosis

The definitive diagnosis of fascioliasis is made by observing eggs in the stool; however, only a small number of eggs reach the stool, requiring multiple examinations for this method. Because of these limitations, serologic studies used during the acute phase before stool examination can yield a diagnosis. Antibodies to *Fasciola* can be detected by Falcon assay screening test—ELISA during the acute phase and is routinely used for initial diagnosis. Eosinophilia is also seen in 95% of acute infections and is a helpful complementary laboratory finding.^{33,34}

CESTODE INFECTION

Key points

- Cestode infections range from asymptomatic to potentially life threatening
- Cutaneous manifestations of sparganosis infection include a solitary, slow-growing, often slowly migrating subcutaneous mass of the anterior abdominal wall
- Cutaneous manifestations of echinococcus and cystercosis infections are rare, but some patients present with subcutaneous nodules

Cestodes (tapeworms) are flat, hermaphroditic parasites that primarily affect the human gastrointestinal tract as adults. In the larval stage, they cause cysts in various human tissues, including the skin. Cestodes are distinguished from trematodes by their lack of an intestine. Cestode infections with mucocutaneous manifestations are reviewed here; treatment is also reviewed (Table I).

SPARGANOSIS

Key points

- Sparganosis is caused by the consumption of contaminated undercooked meat or by direct larval penetration through the skin
- While ocular disease is the most common presentation in sparganosis, cutaneous findings are occasionally seen as a solitary, slow-growing, migrating subcutaneous nodule located on the anterior abdomen
- Surgical excision of the larvae is the treatment of choice because there is no current effective pharmacologic therapy

Sparganosis is caused by the genus *Spirometra*, with a complex 3-host life cycle that ordinarily does not include humans. The typical definitive hosts in which *Spirometra* completes the sexually



Fig 6. Patient infected with *Sparganum proliferum*. Note the multiple skin lesions that are mostly papular and nodular. Linear elevations suggest the shape of the worm beneath the skin. (Courtesy of the American Society of Tropical Medicine and Hygiene.)

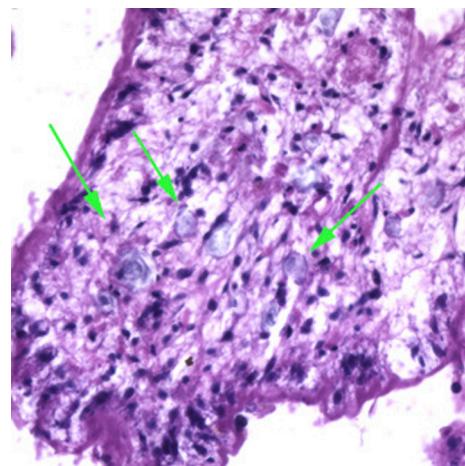


Fig 7. High magnification of proliferating sparganum in lung tissue with calcified granulomas (green arrows). (Courtesy of the Centers for Disease Control and Prevention.)

reproductive phase of its life cycle are carnivores, usually dogs and cats. Occasionally, a human consumes an infected intermediate host and becomes a paratenic host.³⁹ Most human cases of sparganosis occur in Southeast Asia and East Africa, where exposure to or consumption of infected intermediate hosts occurs most commonly. One case series noted 28% (7/25) of patients diagnosed with sparganosis presenting with cutaneous disease.⁴⁰

Life cycle

The adult parasites attach to the intestinal wall and generate typical segments, called proglottids, that are seen in cestode tapeworms.⁴¹ Proglottids release eggs into feces, which are then deposited into an aquatic environment. There the eggs hatch into ciliated, motile forms that are eaten by copepods, a group of minute arthropods often called water fleas. Within the

copepods, the hatched forms continue their larval development into the procercoïd-phase. Infected copepods are then eaten by fish, amphibians, or reptiles, which serve as the second intermediate host. There, the procercoïd larvae penetrate into the animal's subcutaneous tissues, muscles, or central nervous system to develop into more advanced larvae called plerocercos. These intermediate hosts are then eaten by a predator, such as a cat or dog. Once in the carnivore's intestine, the plerocercoid larvae are released from the host's flesh, mature into adults, partake in sexual reproduction, and the life cycle continues.

Humans acquire the parasite via accidental ingestion of water containing procercoïd-infected copepods or undercooked plerocercoid-infected vertebrates. Once inside the digestive tract, the plerocecoïd larvae penetrate the intestinal wall and migrate to other tissues, including muscle, skin, orbits, and brain. Transmission via direct penetration of the larvae can also occur during application of the raw flesh of a plerocercoid-infected vertebrate onto their skin for medical treatment, migrating to other areas of the body afterwards. While sparganum can live up to 20 years inside human hosts, they do not undergo further development.

Presentation

Ocular disease is the most common presentation, presenting as an extraocular (eyelid) mass. Subcutaneous tissue involvement is typically a solitary, slow-growing, often slowly migrating subcutaneous mass of the anterior abdominal wall.⁴¹ Diagnosis of the disease is difficult because it mimics many other conditions that cause subcutaneous nodules.⁴² The epidermis appears normal. *Sparganum proliferum* is the most pathogenic Spirometra species and causes a more disseminating infection than classic sparganosis, resulting in a more diffuse, erythematous nodulopapular rash (Fig 6).⁴³

Diagnosis

Diagnosis is made by eosinophilia and eosinophilic and/or suppurative granulomatous panniculitis. Histologically, there is a granulomatous panniculitis and dermatitis, with a section of a sparganum (Fig 7).⁴⁴ ELISA serologic studies are available using sparganum-specific monoclonal antibodies. The worm is usually <10 cm in length but can be up to 70 cm. The worm is typically white, wrinkled, and ribbon shaped.

CYSTICERCOSIS AND ECHINOCOCCOSIS

Key points

- Cysticercosis is acquired by the consumption of undercooked pork contaminated



Fig 8. Subcutaneous nodules in the lateral aspect of the neck of a patient with cysticercosis.

with the tapeworm *Taenia solium*; echinococcosis is typically associated with contact with infected dogs and sheep

- Skin findings in cysticercosis and echinococcosis are both characterized by multiple, usually asymptomatic subcutaneous nodules/cysts**
- Care must be undertaken during surgical excision of the cysts to avoid anaphylaxis from spillage of larvae**

Cysticercosis and echinococcosis are among the most common human cestode infections. In humans, they cause primarily gastrointestinal symptoms. In cysticercosis, cysts can develop in almost any organ, including the skin. Neurocysticercosis is a leading cause of epilepsy in the developing world and has become an increasingly important health issue in the United States, most notably in the southwest.⁴⁵ In echinococcosis, cysts may be single or multiple, and the skin is involved in <2% of patients.³⁵

Cysticercosis is an infection resulting from the larval form of the pork tapeworm *Taenia solium*. The disease has worldwide distribution, but is considered endemic in Mexico, Africa, Southeast Asia, Eastern Europe, and Central and South America.⁴⁶ The frequency of diagnosis of cysticercosis has been increasing in developed countries because of increased immigration from endemic areas.

Echinococcosis is a zoonosis caused by *Echinococcus* species. The definitive hosts are dogs, and humans are only infected by the larval form. The disease occurs primarily in tropical and subtropical areas, most commonly found in Brazil, Asia, and both North and East Africa.⁴⁷

Life cycle

In the normal life cycle of *T solium*, humans are definitive hosts and pigs are intermediate hosts.



Fig 9. Erythematous and tender subcutaneous nodule of cysticercosis.

Humans usually become infected by consuming raw or undercooked pork that has been infected with the larvae (cysticerci) or by autoinfection from the anus to the mouth. After ingestion, the cysticerci reach the human intestinal tract, where they develop into an adult tapeworm. The adult form attaches to the intestinal wall via a specialized head called a scolex, where it can grow up to 3 to 6 mm long and remain viable for several years. Gravid proglottids release eggs that are excreted in human feces; proglottids themselves can also be excreted in this manner. Animals such as pigs or sheep become infected by ingesting food or substances contaminated with feces; in these hosts, eggs develop into larvae which penetrate the intestinal wall and migrate to striated muscle, where they become cysticerci. Humans can also ingest food contaminated with feces containing eggs. In humans, eggs develop into larvae and further develop into adults within the intestinal tract; larvae can also penetrate through the intestinal wall and reach other tissues, including muscle, brain, skin, and the eyes.

In echinococcosis, adult tapeworms (typically 3-6 mm long) reside in the small bowel of the host—either a human or other host, such as a dog or sheep. Gravid proglottids release eggs that are excreted in the feces. Ingestion of the eggs by a susceptible intermediate host allows the eggs to develop into larvae, which are called oncospheres. In the small intestine, the oncospheres penetrate the mesenteric vessels from which they reach various organs—most notably the liver and the lungs. Here,

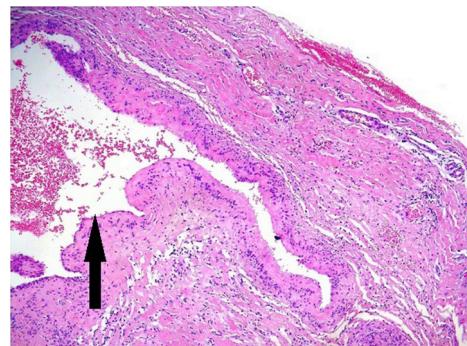


Fig 10. Histologic examination of an excised cysticercosis nodule reveals a cystic structure at the reticular dermis (arrow). Fibrous connective tissue and an inflammatory infiltrate of eosinophils surround the cyst. (Hematoxylin-eosin stain; original magnification: ×40.)

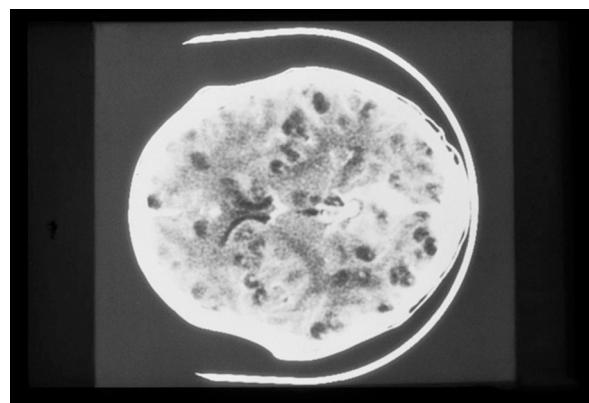


Fig 11. Computed tomography of the head revealing multiple lucencies throughout the cerebral parenchyma representing cysts in a patient with neurocysticercosis. (Courtesy of the American Society of Tropical Medicine and Hygiene.)

the cysts increase in size at a rate of about 1 cm per year.⁴⁸

Presentation

Cysticercosis is characterized by subcutaneous nodules that are usually multiple and asymptomatic. The time from infection to the appearance of subcutaneous nodules is highly variable (range, 1 month to 27 years). These firm, elastic, round, commonly painless nodules resemble other common cutaneous lesions like lipomas, fibromas, and epidermoid cysts (Figs 8 and 9).⁴⁹⁻⁵¹ Patients can also present with palpable intramuscular cysts.⁵² Other symptoms in cysticercosis can be seen, depending on the location of the tapeworm. Neurocysticercosis can present with seizures. Abdominal pain, anorexia, and weight loss can occur because of malabsorption or other digestive problems caused by the presence of the

tapeworm in the intestinal tract. Cysticerci in striated muscle can lead to edema, pain, and fevers.

In echinococcosis, the cysts may be single or multiple and are primarily in the liver and lung. The skin is involved in 2% of patients. Patients may experience urticaria, wheezing, or even anaphylaxis caused by antigens in leaking cyst fluid. Soft tissue cysts may present as subcutaneous nodules that are fluctuant and nontender.

Diagnosis

A definitive diagnosis of subcutaneous cysticercosis is made only by obtaining and reviewing a biopsy specimen and by histologic identification of the cysticercus. A scolex may not always be in the plane of the section, although definitive identification of detached hooklets, scolex, and fragments of the spiral wall of *Cysticercus cellulosae* on fine-needle aspiration smears has been documented in the literature. Fine-needle aspirates of palpable nodules from cysticercosis can reveal findings related to parasitic fragments upon cytologic examination. These include bluish fibrillary structures, sometimes with honeycombing, tegument of parasite thrown into rounded wavy folds, and the scolex with hooklets and surrounding hyaline membrane (Fig 10). Other tests, such as radiographic and immunologic studies, provide indirect evidence of infection. Neurocysticercosis can be detected by a computed tomography scan, with characteristic calcifications and small, dark lucencies representing cysticerci found on imaging (Fig 11).⁴⁵

Echinococcosis is diagnosed based on the radiographic detection of cysts via ultrasound, computed tomography scan, or a magnetic resonance imaging scan. Histologic examination of the cyst with identification of the parasite provides confirmation of the diagnosis. Western blot and enzyme immunoassays are other diagnostic modalities.

CONCLUSION

In conclusion, trematode and cestode infections are considered rare and exotic in America. It is, however, extremely important for the dermatologist to be aware of these conditions given that 5 million Americans are infected with ≥ 1 more tropical disease. Little research has been conducted to understand the burden of these diseases within the United States.⁵³ Several of these conditions have mucocutaneous manifestations as reviewed here. Schistosomiasis has a worldwide distribution and can be prevented by avoiding contact with cercariae-infested water. Paragonimiasis and fascioliasis are food-borne trematodiases that can be avoided by avoiding undercooked or raw seafood. Control of

human waste is important for the prevention of cysticercosis. Meat inspection for *T solium* decreases its prevalence. Echinococcus infection can be decreased by keeping dogs from carcasses of sheep, cattle, and hogs.

REFERENCES

- Doherty JF, Moody AH, Wright SG. Katayama fever: an acute manifestation of schistosomiasis. *BMJ*. 1996;313:1071-1072.
- Harries AD, Cook GC. Acute schistosomiasis (Katayama fever): clinical deterioration after chemotherapy. *J Infect*. 1987;14:159-161.
- Chai JY. Praziquantel treatment in trematode and cestode infections: an update. *Infect Chemother*. 2013;45:32-43.
- Millan JC, Mull R, Freise S, Richter J. The efficacy and tolerability of triclabendazole in Cuban patients with latent and chronic *Fasciola hepatica* infection. *Am J Trop Med Hyg*. 2000;63:264-269.
- Meric R, Ilie MI, Hofman V, et al. Disseminated infection caused by *Sparganum proliferum* in an AIDS patient. *Histopathology*. 2010;56:824-828.
- Wortman PD. Subcutaneous cysticercosis. *J Am Acad Dermatol*. 1991;25(2 pt 2):409-414.
- Steurer S, Auer H. Primary cystic echinococcosis in the subcutaneous gluteal region - a case report. *Wien Klin Wochenschr*. 2008;120(suppl 4):101-103.
- Davis A. Schistosomiasis. In: Farrar J, Hotez P, Junghanss T, et al, eds. *Manson's tropical diseases*. 23rd ed. London: Saunders; 2009:1425-1460.
- Nicolls DJ, Weld LH, Schwartz E, et al. Characteristics of schistosomiasis in travelers reported to the GeoSentinel Surveillance Network 1997-2008. *Am J Trop Med Hyg*. 2008;79:729-734.
- Kupferschmidt K. A worm vaccine, coming at a snail's pace. *Science*. 2013;339:502-503.
- Pinheiro CS, Martins VP, Assis NR, et al. Computational vaccinology: an important strategy to discover new potential *S. mansoni* vaccine candidates. *J Biomed Biotechnol*. 2011;2011:503068.
- Centers for Disease Control and Prevention website. Parasites - schistosomiasis biology. Available at: <http://www.cdc.gov/parasites/schistosomiasis/biology.html>. Accessed May 1, 2014.
- Arnon R. Life span of parasite in schistosomiasis patients. *Isr J Med Sci*. 1990;26:404-405.
- Lucey DR, Maguire JH. Schistosomiasis. *Infect Dis Clin North Am*. 1993;7:635-653.
- Tremaine AM, Whittemore DE, Gewirtzman AJ, et al. An unusual case of swimmer's itch. *J Am Acad Dermatol*. 2009;60:174-176.
- Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. *Lancet*. 2006;368:1106-1118.
- Davis-Reed L, Theis JH. Cutaneous schistosomiasis: report of a case and review of the literature. *J Am Acad Dermatol*. 2000;42:678-680.
- Leman JA, Small G, Wilks D, Tidman MJ. Localized papular cutaneous schistosomiasis: two cases in travellers. *Clin Exp Dermatol*. 2001;26:50-52.
- Ramdial PK, Calonje E, Singh B, et al. Extra-anogenital bilharziasis cutanea tarda revisited. *J Cutan Pathol*. 2009;36:766-771.
- Kjetland EF, Hegertun IE, Baay MF, et al. Genital schistosomiasis and its unacknowledged role on HIV transmission in the STD intervention studies. *Int J STD AIDS*. 2014;25:705-715.
- Al-Karawi KS, Al-Amro Al-Akloby OM, Mugharbel RM. Ectopic cutaneous schistosomiasis. *Int J Dermatol*. 2004;43:550-551.

22. Dainichi T, Nakahara T, Moroi Y, et al. A case of cutaneous paragonimiasis with pleural effusion. *Int J Dermatol.* 2003;42: 699-702.
23. Zarrin-Khameh N, Citron DR, Stager CE, Laucirica R. Pulmonary paragonimiasis diagnosed by fine-needle aspiration biopsy. *J Clin Microbiol.* 2008;46:2137-2140.
24. Malvy D, Ezzedine KH, Receveur MC, et al. Extra-pulmonary paragonimiasis with unusual arthritis and cutaneous features among a tourist returning from Gabon. *Travel Med Infect Dis.* 2006;4:340-342.
25. Centers for Disease Control and Prevention. Human paragonimiasis after eating raw or undercooked crayfish—Missouri, July 2006–September 2010. *MMWR Morb Mortal Wkly Rep.* 2010; 59:1573-1576.
26. Centers for Disease Control and Prevention website. Parasites - paragonimiasis (also known as paragonimus infection). Available at: <http://www.cdc.gov/parasites/paragonimus>. Accessed May 4, 2014.
27. Johnson RJ, Jong EC, Dunning SB, et al. Paragonimiasis: diagnosis and the use of praziquantel in treatment. *Rev Infect Dis.* 1985;7:200-206.
28. Ashitani J, Kumamoto K, Matsukura S. *Paragonimiasis westermani* with multifocal lesions in lungs and skin. *Intern Med.* 2000;39:433-436.
29. Singh TS, Devi KhR, Singh SR, Sugiyama H. A case of cutaneous paragonimiasis presented with minimal pleuritis. *Trop Parasitol.* 2012;2:142-144.
30. Kusner DJ, King CH. Cerebral paragonimiasis. *Semin Neurol.* 1993;13:201-208.
31. Cha SH, Chang KH, Cho SY, et al. Cerebral paragonimiasis in early active stage: CT and MR features. *AJR Am J Roentgenol.* 1994;162:141-145.
32. Cox FE. History of human parasitology. *Clin Microbiol Rev.* 2002;15:595-612.
33. Furst T, Duthaler U, Sripa B, et al. Trematode infections: liver and lung flukes. *Infect Dis Clin North Am.* 2012;26: 399-419.
34. Centers for Disease Control and Prevention website. Parasites - fascioliasis (Fasciola infection). Available at: <http://www.cdc.gov/parasites/fasciola/>. Accessed May 4, 2014.
35. Nelson S, Warschaw K. Protozoa and worms. Chapter 83. In: Bologna J, Jorizzo J, Schaffer J, et al, eds. *Dermatology*. 3rd ed. Philadelphia (PA): Saunders; 2012:1391-1421.
36. Yi-Zhu X, Zhi-Bang Y. A case of ectopic fascioliasis in the skin. *Trop Doct.* 2010;40:253-254.
37. Garcia R, Arrese JE, Ugarte G, Piérard GE. The clinical case of the month. Cutaneous fascioliasis [in French]. *Rev Med Liege.* 2004;59:552-554.
38. Xuan le T, Hung NT, Waikagul J. Cutaneous fascioliasis: a case report in Vietnam. *Am J Trop Med Hyg.* 2005;72:508-509.
39. Taylor RL. Sparganosis in the United States. Report of a case. *Am J Clin Pathol.* 1976;66:560-564.
40. Mo ZS, Li XH, Lei ZY, Xie DY. Clinical analysis of 25 sparganosis cases [in Chinese]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi.* 2013;31:218-220.
41. Centers for Disease Control and Prevention website. Sparganosis. Available at: <http://www.cdc.gov/dpdx/sparganosis/index.html>. Accessed May 4, 2014.
42. Duggal S, Mahajan RK, Duggal N, Hans C. Case of sparganosis: a diagnostic dilemma. *Indian J Med Microbiol.* 2011;29:183-186.
43. Schauer F, Poppert S, Technau-Hafsi K, et al. Travel-acquired subcutaneous *Sparganum proliferum* infection diagnosed by molecular methods. *Br J Dermatol.* 2014;170:741-743.
44. Griffin MP, Tompkins KJ, Ryan MT. Cutaneous sparganosis. *Am J Dermatopathol.* 1996;18:70-72.
45. DeGiorgio CM, Medina MT, Duron R, Zee C, Escueta SP. Neurocysticercosis. *Epilepsy Curr.* 2004;4(3):107-111.
46. Willingham AL, Engels D. Control of *Taenia solium* cysticercosis/taeniosis. *Adv Parasitol.* 2006;61:509-566.
47. Jenkins DJ, Romig T, Thompson RC. Emergence/re-emergence of *Echinococcus spp.*—a global update. *Int J Parasitol.* 2005;35:1205-1219.
48. Centers for Disease Control and Prevention website. Parasites - echinococcosis. Available at: <http://www.cdc.gov/parasites/echinococcosis/biology.html>. Accessed May 4, 2014.
49. Machado-Pinto J. Cestodes. In: Lupi O, Tyring S, Hengge U, eds. *Tropical dermatology*. Philadelphia (PA): Elsevier; 2006:81-85.
50. Uthida-Tanaka AM, Sampaio MC, Velho PE, et al. Subcutaneous and cerebral cysticercosis. *J Am Acad Dermatol.* 2004;50(2 suppl):S14-S17.
51. Miura H, Itoh Y, Kozuka T. A case of subcutaneous cysticercosis (*Cysticercus cellulosae* cutis). *J Am Acad Dermatol.* 2000; 43:538-540.
52. De N, Le TH. Images in clinical medicine. Multiple palpable cysts. *N Engl J Med.* 2013;368:2125.
53. Hotez PJ. Neglected infections of poverty in the United States of America. *PLoS Negl Trop Dis.* 2008;2:e256.

Answers to CME examination

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