**Overall 2019 Conference Needs Assessment**

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**Program Overview**

The Caribbean Dermatology Symposium, presented annually since 2002, is designed to provide high-quality continuing medical education featuring the latest updates in medical dermatology and the diagnosis and treatment of various dermatological conditions. The educational content is of interest to practicing dermatologists, dermatology residents, primary care physicians, as well as nurses and physician assistants who treat dermatological conditions.

Dermatologists and other health care professionals need comprehensive knowledge of the latest developments and techniques in diagnosing and treating skin diseases to ensure the highest standards of patient care. For the 18th Annual Caribbean Dermatology Symposium, an internationally-known faculty and key thought leaders will present in-depth education and stimulate audience discussion on topics including:

* Acne
* Actinic Keratosis and Squamous Cell Carcinoma
* Atopic Dermatitis and Eczema
* Contact Dermatitis/Allergens
* Dermoscopy
* Inflammatory Disease in Pediatric Patients
* Moles and Melanoma
* Onychomycosis and Tinea
* Pathophysiology of Dermatologic Diseases
* Photodermatoses
* Psoriasis
* Public Health and Dermatology
* Rosacea
* Scars/Keloids
* Urticaria

Each session of the Caribbean Dermatology Symposium will include the most up-to-date clinical information that dermatologists and other health providers will find immediately useful in improving patient care.

**Learning Objectives**

**At the conclusion of this live activity, participants should be better able to:**

* Design a comprehensive, evidence-based therapeutic strategy for treating acne.
* Discuss the clinical relevance of emerging science concerning the pathophysiology of acne vulgaris.
* Identify patients at risk for developing actinic keratosis.
* Describe therapeutic approaches to actinic keratosis that optimize efficacy in treating lesions while reducing risk for neoplastic complications
* Apply treatment strategies for atopic dermatitis to achieve therapeutic goals based on the severity of disease.
* Identify the pathophysiological role of inflammatory mediators in atopic dermatitis and their potential as targets for treatment.
* Differentiate among potential causes of contact dermatitis and the treatment approaches required.
* Recognize the role of dermascopy in diagnosis and management of various skin lesions.
* Describe the differences in inflammatory skin conditions between adult and pediatric patients.
* Compare and contrast strategies for managing inflammatory skin disorders in children and adolescents vs those used in adults.
* Distinguish malignant from nonmalignant suspicious neoplasms.
* Design a management plan for melanomas at all stages of development.
* Identify and treat onychomycosis in appropriately selected patients.
* Describe the features, the clinical impact, and key steps in the diagnosis of onychomycosis.
* Compare and contrast the safety and efficacy of onychomycosis treatments, including drug interactions and warnings regarding therapy in patients with comorbid disease or receiving other medications.
* Design effective therapy targeted to address the different forms of tinea.
* Design personalized management strategies that identify and address the specific immunological derangements found in patients with various dermatological conditions.
* Differentiate the various photodermatoses from other dermatologic conditions whose symptoms manifest in similar ways.
* Discuss photoprotection with patients, including pediatric patients and their caregivers.
* Explain the pathophysiological mechanisms that underlie psoriasis and its comorbidities.
* Describe optimal strategies for applying current clinical guidelines in the diagnosis and management of psoriasis.
* Identify patients with psoriasis who may be appropriate candidates for biological therapy.
* Recognize the benefits of community-based preventive strategies aimed at reducing the incidence of skin disease, including cancer.
* Design a comprehensive strategy for the management of rosacea.
* Compare and contrast the benefits and risks of current and emerging therapies for rosacea.
* Discuss techniques for managing keloids that offer the greatest benefit with minimal risk of scarring.
* Tailor stepwise treatment for urticaria that reflects the severity of the disease and the response to therapy of individual patients.

**Evaluations From the 17th Annual Caribbean Dermatology Symposium**

**1. Participating in this educational activity changed my knowledge. N=133**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strongly Agree | Agree | Somewhat Agree | Disagree | Strongly Disagree |
| 40% | 45% | 12% | 2% | 1% |

**2. Participating in this educational activity changed my COMPETENCE. N=133**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strongly Agree | Agree | Somewhat Agree | Disagree | Strongly Disagree |
| 36% | 45% | 15% | 3% | <1% |

**3. Participating in this educational activity changed my PERFORMANCE. N=133**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strongly Agree | Agree | Somewhat Agree | Disagree | Strongly Disagree |
| 29% | 50% | 18% | 3% | <1% |

**4. Based on the content of the activity, what will you do differently in the care of your patients and/or regarding your professional responsibilities? N=133**

|  |  |
| --- | --- |
| **Statement** | **% Responding** |
| Implement a change in my practice/workplace.  | 23% |
| Seek additional information on this topic.  | 21% |
| Implement a change in my practice/workplace and seek additional information on this topic.  | 29% |
| Do nothing differently. Current practice/job responsibilities reflect activity recommendations.  | 26% |
| Do nothing differently as the content was not convincing.  |  0% |
| Do nothing differently. System barriers prevent me from changing my practice/workplace. |  2% |

**Performance Changes from 2018 Conference**

The following comments were provided in response to the request, “If you anticipate changing one or more aspects of your practice and/or professional responsibilities as a result of your participation in this activity, please describe how you plan to do so?”

* Trying some new biologic medication if the right patient comes along. Also enjoyed the reminder to sit with the patients and their view of how long the visit is when the doctor sits vs stands.
* Additional investigation of biologics and possibly start using them.
* New testing for side effects.
* Use new treatments.
* Increase my coding and improve my HPIs.
* I will likely incorporate more biopsies in my practice.
* Maintain good level of care.
* Incorporate sebaceous keratosis surgery and carving of the nose.
* Try new surgical techniques in lecture.
* Change language in chart for skin check.
* Treatment of onychomycosis and psoriasis.
* Better competence with dermoscopy. Seeking more information of AI in my future practice.
* I cooperated photopatch testing in possible photo contact urticaria. Seek further information through journals regarding topics discussed.
* I will work harder to make sure my patients on biologics have a yearly FBE. I will avoid methotrexate in obese patients.
* Excellent overview of how to use biologics; modify treatment of eczema patients.
* I will treat skin of color patients with different products than what I am using now.
* More info on patch testing for the allergen of the year awards.
* Be more aware of atopic dermatitis contact allergen triggers. Be able to educate my patients on top allergens. Have more treatment options for psoriasis, pseudofollicultis barbae and atopic dermatitis.
* Better selection of biologics for psoriasis.

**NEEDS ASSESSMENTS AND GAPS**

**Acne**

**Gap: Many clinicians treat acne without having a complete understanding of the most recent guidelines for diagnosis and management of acne in pediatric, adolescent, and adult populations.**

*Learning objective: Design a comprehensive, evidence-based therapeutic strategy for treating acne.*

Acne is one of the most common skin conditions treated by physicians, affecting 40 to 50 million people in the United States. Although the disease can affect patients at any age, from newborns to the elderly, acne occurs most commonly during the adolescent years, with a prevalence as high as 85%. In 20% of cases the acne is severe, resulting in permanent physical scarring, poor self-image, depression, and anxiety. For this reason, experts recently have broadened the scope of their research, clinical discussions, treatment focus, and guidelines for management to encompass the complete spectrum of the disease.[Zaenglein 2016]

For effective management, all patients with acne, regardless of age, gender, or skin type, need early recognition, accurate diagnosis, and prompt initiation of treatment. Despite the high prevalence of this disease, until recently, guidelines addressing standard management were lacking and approaches to treatment varied widely among clinicians. The situation changed with the publication in 2013 of evidence-based recommendations for the diagnosis and treatment of pediatric acne, developed by a panel from the American Acne and Rosacea Society (AARS) and approved by the American Academy of Pediatrics.[Eichenfield 2013] These comprehensive guidelines are the first to specifically address acne in the pediatric population.

In 2016 the American Academy of Dermatology (AAD) published its guidelines of care for acne vulgaris management in adolescents and adults.[Zaenglein 2016] The guidelines discuss topical and systemic therapies as well as physical modalities, including lasers and photodynamic therapy. In addition, a grading/classification system, microbiology and endocrinology testing, complementary/alternative therapies, and the role of diet are reviewed.

Many clinicians are not sufficiently knowledgeable about the new guidelines to effectively apply them in clinical practice. A recent survey revealed that only 41% of respondents correctly stated that pustular acne was the form of acne that may respond quickly to drying therapy with a combination of benzoyl peroxide and sulfacetamide and sulfur lotion. In the same survey, only 13% of respondents knew that some form of facial scarring has been reported in up to 95% of acne patients. Similarly, only 25% of respondents believed that patients with acne fulminans, and without systemic symptoms, should be treated with prednisone for 2 weeks, according to the guidelines; most would apply this treatment for 4 weeks.[Frontline Medical Communications, MD-IQ quiz, 1/25/2016-8/03/2016]

Clinicians should also take into account the needs of special populations. For example, challenges in managing acne in adult women include patient preferences, pregnancy, and lactation. Treatments vary widely and treatment should be tailored specifically for each individual woman.[Tan 2017] Similarly, topical retinoids are effective but are nonetheless underutilized among patients of Asian descent, due in part to the perception that Asian skin is more sensitive to these agents than is Caucasian skin.[See 2018] As a result, such agents may be underutilized in this population.

**Gap: Due to an incomplete understanding of the basic etiologies for acne and lack of confidence in prescribing, many clinicians fail to use advanced or appropriate treatment modalities in acne patients.**

*Learning objective: Discuss the clinical relevance of emerging science concerning the pathophysiology of acne vulgaris.*

The AAD guidelines [Zaenglein 2016] and those from the European Dermatology Forum (EDF) [Morton 2015] agree that retinoids have an essential role in treatment of acne. The AAD states that retinoids are the core of topical therapy for acne because they are comedolytic, anti-inflammatory, and allow for maintenance of clearance.[Zaenglein 2016]

Despite uniform recommendation for use of topical retinoids, a recent study of prescribing practices from 2012 to 2014 indicated that dermatologists prescribed retinoids just 58.8% of the time while non-dermatologists prescribed them for only 32.4% of cases.[Leyden 2017] Another report suggested that fewer than half of clinicians treating pediatric patients self-reported confidence in prescribing according to the AARS guidelines, particularly in selecting combination therapy for patients with moderate to severe acne.[Feldstein 2016]

Fortunately, many effective treatment strategies are now available to manage acne vulgaris in younger patients. Safe and effective topical and oral therapies are approved for patients as young as 12 years of age. In 2014, the FDA approved clindamycin phosphate and benzoyl peroxide 1.2%/3.75% for once-daily treatment of comedonal and inflammatory acne in patients 12 and older.

The common perception among clinicians is that the microcomedone is the initiating event in the development of all acne lesions. However, technically speaking, all lesions are inflammatory lesions; inflammation may be a primary event in acne, and may persist throughout the lesion lifecycle, even beyond the disappearance of visible lesions.[Stein Gold, 2017] Emerging therapies and regimens offer clinicians an enhanced range of options to improve tolerability, sustain positive clinical outcomes, and effectively treat diverse patient populations. For patients with moderate to severe and persistent acne, oral and topical antibiotics have been the therapies of choice. Recent reports have suggested the superiority of combination therapy with topical treatments (such as tretinoin and other retinoids, benzoyl peroxide, and salicylic acid), for mild-to-moderate comedonal lesions, superficial inflammatory (papular or pustular), and nonscarring acne.[Stein Gold, *Semin Cutan Med Surg. 2016*]

Photodynamic therapy (PDT) is an effective adjunctive treatment for mild to severe acne, especially in patients who have not responded to topical therapy and oral antibacterials and who are not good candidates for isotretinoin, according to a recent review.[Boen 2017] The most common photosensitizers used in this report were 5-aminolevulinic acid and methyl aminolevulinate, and red light plus intense pulsed light was the most common light source. Inflammatory and non-inflammatory lesions both responded to the treatment, with inflammatory lesions showing greater clearance in most studies. The use of newer types of lasers, such as those used to remove tattoos (picowavelength lasers) in acne scar removal, is under study.[Mechcatie 2017]

Systemic treatments (such as the tetracycline class of oral antibiotics) are indicated for moderate to severe manifestations (scarring or nonscarring) and patients with persistent hyperpigmentation. However, emerging data suggest limiting the use of oral antibiotics in patients with acne, particularly children.[Stein Gold *2016*] Other treatments, including oral isotretinoin, light-based phototherapy, and laser therapies, may be as effective for carefully selected patients.[Zaenglein 2016]

Other therapies have shown efficacy in adult women with acne. A 4-year retrospective study reported that up to 95% of adult women with acne improved on spironolactone alone or in combination with a topical agent.[Grandhi 2017] In another study, topical spironolactone gel improved the non-inflammatory elements of mild to moderate acne in adult women.[Bagherani 2014] Oral contraceptives have also shown efficacy in treating acne in adult women.[Harper 2015]

Several new agents are emerging that may reduce sebum production: SB204, a topical agent, releases nitric oxide, which has antimicrobial and anti-inflammatory activities and may also reduce sebum production. A second drug, DRM01, targets acetyl coenzyme-A carboxylase (ACC), which is a key regulator of sebum production. A third topical agent is a potent antiandrogen, CB-03-01 (cortexolone 17α-propionate 1%), which has shown at least comparable efficacy to tretinoin.[Stein Gold 2016]

Ongoing education of clinicians is needed with respect to new research findings on acne pathogenesis, disease course, and current treatment guidelines. Clinicians also must be kept up to date as new agents and newer formulations and delivery routes for existing medications are developed. Antimicrobials, including odified diallyl disulfide oxide and nitric oxide, are under investigation as potential acne therapies.[Trivedi 2018] Also being studied are anti-inflammatory phytochemicals; small molecule inhibitors targeting sebaceous glands and enzymes; laser light therapy in combination with metal nanoshells and vacuum assistance; and probiotics that alter the microbiome.[Trivedi 2018]

Clinicians would benefit from education that keeps them abreast of scientific developments and their potential application in the management of acne.

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**Actinic Keratosis and Squamous Cell Carcinoma**

**Gap: Dermatologists treating patients must be able to recognize and treat nonmelanoma skin cancers and actinic keratoses as early as possible, including appropriate follow-up care, to minimize the risk for developing skin cancers.**

*Learning objective: Identify patients at risk for actinic keratosis.*

Actinic keratosis (AK) – a skin lesion resulting from sun exposure – is the second most common diagnosis in dermatologic practices, affecting more than 58 million Americans. Despite its prevalence, there is no universally accepted definition of AK and thus it may be difficult to identify reliably.[Siegel 2017] The condition is especially prevalent among patients with skin phototypes I or II, or with specific genetic factors and who are exposed to prolonged ultraviolet radiation.[Arenberger 2017] AK poses a significant risk of progressing to squamous cell carcinoma (SCC). The rate of progression from AK to cutaneous SCC is estimated to be between 0.025% and 16% per year for an individual lesion; however, because a person with AK typically has 6 to 8 lesions, the inherent risk of progression is between 0.15% and 80%. It is still not possible to predict which AK lesions will progress to SCC.[Arenberger 2017] For this reason, both clinically visible lesions and subclinical, non-visible lesions (ie, the entire area affected by AK/field cancerization) should be treated.[Goldenberg 2017] An estimated 700,000 cases of SCC are diagnosed each year in the United States, resulting in approximately 2,500 deaths. Well-established clinical criteria are lacking that would help clinicians determine which specific AK lesions are most likely to undergo malignant transformation.

About 90% of nonmelanoma skin cancers (NMSCs) are associated with exposure to ultraviolet radiation from the sun. Despite widespread and ongoing educational efforts about this risk, at least 50% of children and adults still do not adequately protect themselves from exposure, failing to use simple measures such as wearing proper clothing and applying sunscreen. It has been estimated that regular application of sunscreen with a sun protection factor of 15 or greater for the first 18 years of life would reduce the lifetime incidence of NMSC by 78%. Other risk factors for NMSCs include having a fair complexion, genetic and molecular alterations, and immunosuppression.[Didona 2018] Awareness of these factors can lead to more effective prevention of NMSC.[Didona 2018]

**Gap: Clinicians must be aware of the new formulations of existing actinic keratosis and squamous cell carcinoma treatments, as well as new compounds—in particular, biologic agents—that currently are being evaluated in clinical trials and should be prepared to assess the emerging data on these new therapies.**

*Learning objective: Describe therapeutic approaches to actinic keratosis that optimize efficacy in treating lesions while reducing risk for neoplastic complications.*

The major treatment options for AK include destructive therapies (eg, cryotherapy, surgery, dermabrasion), topical medications (eg, 5-fluorouracil [5-FU], imiquimod, ingenol mebutate, diclofenac), chemical peels (eg, trichloroacetic acid), and photodynamic therapy (PDT). Given that multiple effective treatment options are available for AK, the choice of therapy is influenced by several factors including the number and distribution of lesions, lesion characteristics, patient preference for the mode of treatment (eg, office-based versus home administered, duration of therapy), patient tolerance for side effects (eg, pain, inflammation, hypopigmentation, scarring), treatment cost, and treatment availability.[Goldenberg 2017]

Recent research has identified several promising approaches to treating AK and SCC. A steroidal alkaloid extracted from the corn lily *Veratrum californicum* inhibits the hedgehog signaling pathway, mediated by the tumor suppressor patched (PTCH) and the proto-oncogene smoothened (SMO) genes. Nicotinamide (vitamin B3 or niacinamide) is a substrate and inhibitor of poly-ADP-ribose polymerase and a precursor of nicotinamide adenine dinucleotide, both of which are involved in DNA repair. Orally administered nicotinamide has shown to significantly reduce rates of new NMSC and AK in high-risk patients.[Arenberger 2017] A new formulation containing a low dose of fluorouracil (0.5%) to decrease adverse events and salicylic acid (10%) to reduce hyperkeratosis and increase penetration of fluorouracil through the skin is currently being marketed in several European countries for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis in immunocompetent adult patients. Further larger studies are needed before considering any of these new options as an effective agent for the reduction of AKs.

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**Atopic Dermatitis**

**Gap: Clinicians need to improve their knowledge of current diagnostic guidelines and treatment paradigms for atopic dermatitis (AD) and to develop strategies for incorporating these approaches into their clinical practice.**

*Learning objective: Apply treatment strategies for atopic dermatitis to achieve therapeutic goals based on the severity of disease.*

Atopic dermatitis (AD), also called eczema, is a chronic, relapsing inflammatory skin disease that is associated with significant morbidity and costs to patients and their families. The prevalence of AD in the United States is 3%-5% overall, with a higher prevalence in children (10%-15% lifetime), varying by geographical location. The prevalence in children has increased by as much as 30% in recent decades.[Eichenfield & Stein Gold 2017] Adult-onset AD is also on the rise, with a current prevalence in the United States as high as 7%-10%.[Splete H 2017]

The evidence-based guidelines for the diagnosis and assessment of AD, published in 2014, provide criteria for accurately diagnosing and differentiating AD from other conditions with similar characteristics.[Eichenfield 2014] Clinicians need to become aware of these guidelines so as to be better able to recognize AD, distinguish it from other conditions with similar appearance, and initiate effective treatment at the earliest opportunity.

Diagnosis of AD is based on typical findings including pruritus, erythema, papules/vesicles, xerosis, excoriations, erosions, and often lichenification and dyspigmentation. In infants, the face (particularly the cheeks and chin), trunk, and extensor extremities are the most common sites of involvement, with sparing of the diaper area. In toddlers and older children, the most commonly affected sites are the flexoral areas of the wrists, ankles, and antecubital and popliteal fossae. In adolescents and adults, the wrists, hands, neck, and ankles are typically affected.[Eichenfield 2017]

Clinicians need to be alert to potential misdiagnosis of adult AD as contact dermatitis. Differential diagnosis includes ichthyosis vulgaris, keratosis pilaris, nummular dermatitis, psoriasis, scabies, seborrheic dermatitis, and tinea corporis. Findings that should prompt reconsideration of the diagnosis of atopic dermatitis in infants and young children include failure to thrive; multiple cutaneous and/or systemic infections; unusual morphology or distribution of rash; poor response to typical atopic dermatitis treatments; fixed-plaque hypopigmentation; and late onset AD signs and symptoms.[Eichenfield and Stein Gold 2017]

Pruritus and other signs and symptoms associated with the disease can be severe and their impact on quality of life significant, particularly in those with moderate to severe disease. Coping with AD can lower self-esteem, negatively affect school performance and social interactions, disrupt sleep, and generally increase day-to-day stress experienced by patients and their families.[National Eczema Association] Although AD is common and relatively easy to identify, clinicians should avoid being complacent about the disease and its management. Additionally, there are often gaps between evidence-based guidelines in AD management, what the clinician recommends, and what the patient does.[O'Toole 2013]

Before seeking evidence of concomitant sensitivities such as foods and environmental allergens, clinicians can better identify the diagnostic and therapeutic path in AD by closely questioning patients and their families about the lesions, symptoms, and impact of their condition.[Eichenfield 2017] Indeed, specialized testing for sensitivities or blindly eliminating common allergenic foods from the diets of all patients with AD is generally not effective in modifying disease course. Nevertheless, some patients may have comorbid food allergies, and referral to a pediatric allergist is appropriate when skin disease is recalcitrant and the patient has a history of exacerbation after exposure to certain foods. [Stein Gold and Eichenfield 2017]

Clinicians need to become more conversant with the growing armamentarium of available therapeutic agents, their indications, and their appropriate use to achieve optimal clearing of skin lesions. Well-established treatment options such as emollients, corticosteroids, and topical calcineurin inhibitors will continue to play a role in treating AD of all severity levels. The use of topical corticosteroids to bring an acute flare under control is an established strategy, and research supports corticosteroid maintenance after clearing. In one study, ongoing maintenance with low-dose fluticasone propionate plus moisturizers for 4 weeks reduced the risk of relapse at 20 weeks.[Hanifin 2002] Another option is the use of the topical calcineurin inhibitors (TCIs) pimecrolimus and tacrolimus – corticosteroid-sparing agents that have been safely used for many years. Unlike corticosteroids, these agents can be used on any affected body surface including the face. Studies report short- and long-term efficacy of pimecrolimus, which has been approved for use in patients <15 years of age at the 0.03% concentration.[Afshar 2013; Eichenfield J Pediatr 2015; Luger 2015; Stein Gold and Eichenfield 2017]

Recent research into the pathophysiology of AD has revealed a complex etiology involving multiple immunologic and inflammatory pathways. Advances in the understanding of the roles of filaggrin and ceramides (waxy lipid molecules) has led to the theory of barrier therapy and the development of new moisturizers and topical skin therapies that are targeted to increase the levels of ceramides and natural moisturizing factors in the skin.[Miyagaki 2015; Irvine and McLean] The early identification of susceptible patients suggests the possibility of preventing or minimizing the risk for the development of AD. In one report, daily emollient use in susceptible infants beginning at age 3 weeks produced a 50% relative reduction in the risk of AD at age 6 months.[Simpson 2014]

Impairment of epidermal barrier function due to deficiency in the structural protein filaggrin can promote inflammation and T cell infiltration.[Weidinger 2018] With the increasing understanding of the role of epidermal skin barrier defects in AD pathogenesis, moisturization alone has become an option in treating mildly infected eczema. A recent study found rapid resolution in response to topical steroid and emollient treatment and ruled out a clinically meaningful benefit from the addition of either oral or topical antibiotics in children with mild clinically infected eczema.[Francis NA et al. 2017] Also, dilute bleach baths followed by application of a moisturizer and/or emollient ointment confers anti-inflammatory and anti-infective properties.

A recent review of studies investigating the effectiveness of bleach baths found that they improve the clinical symptoms of atopic dermatitis and restore surface microbiome by eradicating *Staphylococcus aureus* and other bacteria.[Maarouf 2018] This benefit appears to reduce the need for topical corticosteroids or topical antibiotics. Bleach baths do not disrupt the epidermal barrier function, and have strong anti-inflammatory and anti-pruritogenic effects.[Maarouf 2018] However, it is not yet known whether bleach baths, as monotherapy, are sufficient to manage AD.

To address the role of barrier dysfunction in the pathogenesis of AD, therapies that address the underlying lipid biochemical abnormality may be needed. These lipid-based forms of barrier repair therapy have been shown to be as effective as topical mid-potency corticosteroids.[Elias 2018] A novel addition to the topical armamentarium that appears to be gaining momentum involves the application of topical antioxidants (such as furfuryl palmitate) or ceramides.[Draelos 2018; Pigatto 2018] A review of studies regarding the beneficial effects of the new antioxidant molecule furfuryl palmitate (and its derivatives) indicates it is safe and effective in ameliorating the signs and symptoms of mild-to-moderate AD, along with other cutaneous skin disorders.[Pigatto 2018] Similarly, a recent study reported on the benefits of a proprietary therapeutic cream containing ceramides in the management of signs and symptoms of mild-to-moderate AD and other pruritic dermatoses.[Draelos 2018] These agents have no side effects and thus are safe to use in all patient populations.

**Gap: Clinicians need guidance to understand the role of inflammation in the pathogenesis of AD and in the use of current and emerging therapies designed to block the inflammatory activity that produces AD symptoms.**

*Learning objective: Identify the pathophysiological role of inflammatory mediators in atopic dermatitis and their potential as targets for treatment.*

Recent epidemiological, genetic and molecular research has focused interest on skin barrier dysfunction as a common precursor and pathological feature of AD. Current understanding of the etiology of atopic dermatitis highlights disruption of the epidermal barrier leading to increased permeability of the epidermis, pathological inflammation in the skin, and percutaneous sensitization to allergens.[Tsakok 2018]

Thus, most novel treatment strategies seek to target specific aspects of the skin barrier or cutaneous inflammation. Type 2 cytokines interleukin (IL)-4 and IL-13 appear to be key drivers of atopic dermatitis and are likely important drivers of atopic or allergic diseases in general.[Simpson NEJM 2016] Two new medications targeting these mediators were approved by the FDA in 2016 and 2017, and many others are under development (Table).[Eichenfield and Friedlander 2016] One example is tralokinumab, an IL-13 antagonist, now undergoing a phase 3 trial in combination with topical corticosteroids in patients with moderate to severe AD. Upadacitinib, a Janus kinase (JAK) inhibitor, is being studied as a once-daily therapy for AD; having met its primary end point in a phase 2b study, a phase 3 study is now under way.[Frellick 2017]

*New and Emerging Treatments for Atopic Dermatitis*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Status** | **Compound** | **Category** | **Mechanism of Action** | **Administration** |
| Approved | Crisaborole | Small molecule | PDE-4 inhibition | Topical |
| Dupilumab | Biologic | IL-4Ra/IL-13 receptor alpha-chain antagonism | SC injection |
| Phase 3 | Tralokinumab | Biologic | IL-13 antagonism | SC injection |
| Phase 2 | AQX-1125 | Small molecule | SHIP1 activator | Oral |
| ABT-494 | Small molecule | JAK | Oral |
| Apremilast | Small molecule | PDE-4 inhibition | Oral |
| Asimodaline | Small molecule | Kappa-opioid receptor agonism | Oral |
| Baricitinib | Small molecule | JAK 1/2 | Oral |
| Fevipiprant | Biologic | CRTH2 antagonism | Oral |
| GBR 830 | Biologic | Anti-OX40L | IV infusion |
| ILV-094 | Biologic | IL-22 antagonism | IV infusion |
| Ruxolitinib | Small molecule | JAK 1/2 antagonism | Topical |
| Lebrikizumab | Biologic | IL-13 antagonism | SC injection |
| Ligelizumab | Biologic | IgE antagonism | SC injection  |
| Mepolizumab | Biologic | IL-5 antagonism | SC injection |
| Nemolizumab | Biologic | IL-31 receptor antagonism | SC injection |
| Omalizumab | Biologic | IgE antagonism | IV/SC injection |
| OPA-15046 | Small molecule | PDE-4 inhibition  | Topical |
| PF-04965842 | Small molecule | JAK 1 antagonism | Oral |
| Q301 | Small molecule | CRTH2 antagonism | Topical |
| Secukinumab | Biologic | IL-17A antagonism | SC injection |
| Serlopitant | Small molecule | NK1 receptor antagonism | Oral |
| Tezepelumab | Biologic | TSLP antagonism | IV infusion |
| Timapiprant | Biologic | CRTH2 | Oral |
| Tradipitant | Small molecule | NK1 receptor antagonism | Oral |
| Tralokinumab | Biologic | IL-31 receptor antagonism | SC Injection |
| Ustekinumab | Biologic | IL23 p40 antagonism | SC injection |
| LPO 133 | Small molecule | Pan-JAK | Oral |
| Phase 2a | Fezakinumab | Biologic | IL-22 antagonism | SC injection |
| Upadacitinib | Small molecule | JAK 1 antagonism | Oral |
| ZPL-389 | Small molecule | Histamine H4 receptor antagonism | Oral |
| Phase 2b | ARGX-122 | Biologic | IL-22R1 | IV infusion |
| Phase 1 | XmAb7195 | Biologic | IgE antagonism | Injection |
| BMS-981164 | Biologic | IL-31 receptor antagonism | SC injection |
| Segra | Small molecule | Selective glucocorticoid nonsteroidal receptor agonist | Topical |

*CRTH2 = chemoattractant receptor-homologous molecule expressed on T helper cell type 2; IgE = immunoglobulin E; IL = interleukin; IV = intravenous; JAK = Janus kinase; PDE = phosphodiesterase; SC = subcutaneous; TSLP = thymic stromal lymphopoietin.*

*Source: Renert-Yuval Y, et al.*

Crisaborole, a boron-based phosphodiesterase (PDE)-4 inhibitor, was approved in 2016 for the topical treatment of AD. The safety and efficacy of crisaborole ointment 2% were evaluated in 2 vehicle-controlled phase 3 trials in >1500 patients with mild or moderate AD.[Paller 2016] Significantly more crisaborole-treated patients achieved the study endpoints (ISGA of 0 or 1) by day 29 compared to those on vehicle. Treatment-related adverse events included AD and pain at the application site. In an open-label extension, severity of treatment-emergent adverse events was mild or moderate. No cases of application site atrophy, telangiectasia, or hypopigmentation were reported.[Paller et al 2016]

The systemic agent dupilumab was approved for treatment of AD in 2017. An inhibitor of the IL-4 receptor alpha subunit, dupilumab was evaluated in 2 16-week phase 3 placebo-controlled trials in adult patients whose AD was not adequately controlled with topical agents or who were not candidates for topical medication. In both trials, dupilumab produced an improvement of at least 75% on the EASI (EASI-75) at week 16 in significantly more patients compared with placebo (*P*<0.001 for all comparisons). Also in the 2 trials, dupilumab significantly reduced patient-reported symptoms of atopic dermatitis and its effect on sleep, symptoms of anxiety or depression, and quality of life.[Simpson NEJM 2016] A recent 16-week, double-blind, randomized, placebo-controlled phase III trial reported that significantly more adult patients receiving dupilumab 300 mg weekly (qw) or every 2 weeks (q2w) in conjunction with topical corticosteroid (TCS) treatment achieved >75% improvement from baseline in the EASI at week 16 compared with patients receiving placebo with TCS (P<0.001 for both doses vs placebo).[de Bruin-Weller 2018] In addition, patients receiving dupilumab with TCS demonstrated significant improvements in other clinical manifestations – including pruritus, pain, sleep disturbance, psychiatric symptoms (anxiety and depression), and quality of life. Further, no new safety signals were identified, and no significant differences in overall rates of adverse events between the groups.[de Bruin-Weller 2018] A long-term (120 weeks), phase 3 open-label extension study in pediatric patients with AD is underway.

A topical PDE-4 inhibitor, OPA-15406, produced promising results in an 8-week vehicle-controlled phase 2 study in patients 10 to 70 years of age with mild or moderate AD.[Hanifin 2016]. The primary end point, IGA of 0 or 1 with ≥2-grade reduction, was met at week 4 in the group receiving 1% concentration. Mean percentage improvement from baseline EASI score was notable in week 1 (31.4% vs 6.0% for vehicle; *P*=0.0005), was larger in week 2 (39.0% vs 3.0%; *P*=0.0001) and persisted for 8 weeks.

The therapeutic pipeline for atopic dermatitis is rapidly expanding, with a large number of agents currently in phase 2 or 3 clinical trials.[Paller 2017] Current trials include biologics that inhibit Th2 cytokines (thymic stromal lymphopoietin, IL-4, IL-5, IL-13, and IL-31 and their receptors), or Th22/Th17 cytokines.[Paller 2017; Simpson 2017] In addition, orally administered Janus kinase inhibitors- including tofacitinib and PF-04965842- have demonstrated initial benefit,[Cinats 2018; Cotter 2018; Jancin 2015; Paller 2017; PfizerNews 2018] but long-term studies are needed. Agents that address itching (NK1R inhibitors) are also being studied.[Paller 2017] Studies on the leukotriene mediator montelukast have not been consistent, offering only limited evidence of efficacy in treating moderate-to-severe AD.[Chin 2018]

Several studies have also shown promise in preventing atopic dermatitis, such as the early use of emollients in high-risk infants. This may have broader implications in terms of halting the progression to atopic comorbidities including food allergy, hay fever, and asthma.[Tsakok 2018] Although AD has no cure, the current consensus suggests that, with the availability of new medications and better strategies for use of traditional therapies, signs and symptoms of AD can be significantly reduced and flares effectively controlled or even prevented. With the rapid growth of emerging biologic therapies for AD, it is imperative that clinicians remain current on their knowledge of ongoing clinical trials for their patients, as well as new and emerging agents in order to provide optimal care.

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**Contact Dermatitis/Allergens**

**Gap: Clinicians need to assess patients for a range of possible contact irritants/allergens and develop treatment strategies on a personalized basis.**

*Learning objective: Differentiate among potential causes of contact dermatitis and the treatment approaches required.*

Contact dermatitis is divided into irritant contact dermatitis, a nonspecific response of the skin to direct chemical damage that releases mediators of inflammation predominantly from epidermal cells, and allergic contact dermatitis, a delayed (type 4) hypersensitivity reaction to exogenous contact antigens.

About 20% of the general population is contact-sensitized to common haptens such as fragrances, preservatives, and metals; such sensitivity can lead many individuals to develop allergic contact dermatitis.[Martin 2018] This inflammatory skin disease is mediated predominantly by memory T lymphocytes recognizing low-molecular-weight chemicals after skin contact; the innate immune system also plays an important role.[Martin 2018]

Successful contact dermatitis treatment consists primarily of identifying the cause of the reaction. To distinguish among the various types of contact dermatitis and make a diagnosis, clinicians need to consider a number of factors, including tissue morphology, histology, and immunologic findings.[Fonacier] Intriguingly, current research has shown that  different allergens have distinct molecular fingerprinting.[Leonard 2018] For example, nickel promotes strong Th1/Th17 polarization, whereas fragrance allergy causes Th2/Th22 skewing, which is similar to the phenotype of atopic dermatitis. Previously, allergic contact dermatitis was thought be constant across all allergens; new data suggest, however, mechanistically, the disease may manifest in different ways according to the allergen involved.[Leonard 2018] Clinicians would benefit from increased awareness of these differences as the conduct their diagnostic examination and should base their treatment choices on a patient’s unique allergen polarity.[Leonard 2018]

In 2015 the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint, Council of Allergy, Asthma & Immunology issued a practice parameter summarizing the state of art in diagnosing and managing contact dermatitis. This document addresses the increased use of the commercially available T.R.U.E. Test patch testing method as well as advances in such areas as type IV hypersensitivity reactions, emerging contact allergens, irritant contact dermatitis, systemic contact dermatitis, patch testing in children, occupational dermatitis, and reactions to biomedical devices. Besides providing detailed descriptions of the many forms of contact dermatitis and the wide range of approaches to its treatment, the parameter makes recommendations that address avoidance and prevention.[Fonacier]

Recent studies have highlighted differences in reactivity to allergens between black and white individuals.[Deleo] Another report notes a high prevalence of occupational contact dermatitis, particularly among males who work as automobile mechanics.[Warshaw] Several new contact allergens are identified every new year, constantly expanding the horizon of known causes of allergic contact dermatitis.[Martin 2018]

The main strategy for reducing contact dermatitis is to avoid known irritants or allergens. Traditional treatments for contact dermatitis promote skin barrier integrity and resolve the inflammatory component of the condition. In mild cases, this can be achieved by using emollient-based therapy, including barrier creams and wet compresses, which promote skin barrier repair.[Lachapelle 2018] Topical glucocorticosteroids are used in severe cases and are effective in reducing inflammation. Topical immunomodulators are approved for atopic dermatitis and are prescribed for cases of allergic contact dermatitis when they offer safety advantages over topical corticosteroids.[Fonacier] The epidemic of sensitivity to methylisothiazolinone, a synthetic biocide and preservative that is used in numerous personal care products and a wide range of industrial applications, previously documented in Europe, is also occurring in North America.[DeKoven] Furthermore, patch testing with allergens beyond a standard screening tray is necessary for the complete evaluation of occupational and nonoccupational allergic contact dermatitis.

Ongoing basic and clinical research as well as in vitro testing for contact allergen identification, the recognition of the impact of contact dermatitis, and the continuing education and training to raise awareness for prevention and for improvement of workplaces will result in avoidance of hazardous chemicals and improved management of this important skin disease.[Martin 2018]

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**Dermoscopy**

**Gap: Dermoscopy is often underused or misused, leading to missed diagnosis or misdiagnosis.**

*Learning objective: Recognize the role of dermascopy in diagnosis and management of various skin lesions.*

Noninvasive imaging technologies have been found to improve diagnostic accuracy, detect earlier stage melanomas, and reduce costs. Total-body photography and sequential digital dermoscopy imaging, in combination with direct-to-consumer applications and teledermatology, are already revolutionizing the ways in which physicians and patients partner to enhance dermatologic assessment and management. Dermoscopy (also known as dermatoscopy, epiluminescence microscopy, incident light microscopy, and skin-surface microscopy) is a noninvasive, in vivo technique that can enhance the diagnosis of numerous skin conditions; it is particularly beneficial in determining whether or not to biopsy pigmented lesions to distinguish malignancies (melanoma and pigmented basal cell carcinoma) from benign nevi or seborrheic keratoses.[Marghoob 2018; Wachter 2010]

Dermoscopy requires a high-quality lens for significant magnification along with a lighting system to visualize subsurface structures and patterns. Hand-held devices, fluid immersion and polarized dermatoscopes are also available. Studies have identified numerous benefits of dermoscopy, including enhanced accuracy versus clinical diagnosis.[Sinz 2017; Berk-Krauss 2017; Carrera 2018] It can improve diagnostic accuracy by as much as 30% over unaided visual clinical inspection alone.[Braun 2009] Factors that determine the diagnostic accuracy of dermoscopy include experience of the practitioner, diagnostic algorithm and threshold for a positive test, and clinical context/patient-related factors.[Argenziano 2011; Marghoob 2018; Zalaudek 2009]

A variety of evaluation tools are available to aid in the use of dermoscopy. The two-step pattern recognition method requires the dermatologist to first determine if the neoplasm Is a melanocytic proliferative one (eg, nevus or melanoma) and to then use pattern recognition or an algorithm to confirm a diagnosis. The “3-point rule” requires a lesion with any 2 of the 3 criteria (atypical asymmetry, atypical pigment network, or blue-white structures) to be biopsied, because there is a higher likelihood of melanoma. The 7-point algorithm integrates the above 3 criteria with 4 minor criteria: streaks, regression pattern, irregular diffuse pigmentation, and irregular dot and globules in the decision-making process for biopsy. Use of dermoscopy can thus reduce the number of benign lesions excised. With proper training, dermoscopy may eventually result in the referral of fewer benign lesions from primary care physicians, although it may initially increase the number of unnecessary excisions without sufficient training on its use and interpretation of results. Notably, “false positive” results can lead to unnecessary excisions, and “false negative” results might result in overlooking a cancer.[Kamińska-Winciorek 2015; Papageorgiou 2018] Clinicians need training on the use of dermoscopy and interpretation of the findings, including the clues that indicate dermoscopic variations of malignancies versus benign tumors.[Papageorgiou 2018]

According to David L. Swanson, MD, chief of medical dermatology at the Mayo Clinic in Scottsdale, Arizona, “Patients are becoming aware of the technique and more and more are expecting their dermatologists to be skilled in its application.”[Wachter 2010] While dermoscopy is routinely taught to primary care physicians outside the US, such as in Europe and Australia, surveys of US dermatologists (predominantly those in academic medical centers) estimate that dermoscopy training has been provided to anywhere from 17% to 84% of residents.[Charles 2005; Terushkin 2010] A survey of practicing US dermatologists reported that only 48% were using dermoscopy; factors associated with increased use included younger versus established dermatologists, female sex, dermoscopy training, and involvement in resident teaching.[Engasser 2010] The study noted that barriers to dermoscopy use included lack of training, lack of interest, time required for dermoscopic examination, and a belief that dermoscopy would not affect clinical decisions.[Engasser 2010] However, a recent survey found that nearly 81% of participating dermatologists have used dermoscopy, and 83% were trained in it. Notably, about 98% of dermatologists with <5 years in dermatology practice used dermoscopy, and 100% of them had received training in dermoscopy.[Murzaku 2014] However, fewer than one-third of responding dermatologists perform dermoscopy on all pigmented lesions, and just under 50% use sequential dermoscopy imaging with baseline dermoscopy to follow changes in individual lesions.[Murzaku 2014]

In addition to its value in recognizing potentially malignant lesions, use of dermoscopy has been expanding to evaluation of other more general dermatologic conditions, including scalp and hair disorders, onychomycosis, skin infections/infestations (eg scabies), and cutaneous inflammatory diseases.[Errichetti 2015; Micali 2016] The usefulness of dermoscopy in inflammatory dermatoses is particularly promising because it offers a cost-effective, noninvasive tool with rapid results.[Micali 2016]

Integrating dermoscopy into routine clinical practice can enhance diagnostic accuracy of melanoma and other malignancies, as well as other common dermatologic conditions. To achieve these results, and to minimize the risk of inter-individual variability that is inherent to the technique, clinicians need practical education on dermoscopy training.[Marchionda 2010; Marghoob 2018; Halani 2018]

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**Inflammatory Disease in Pediatric Patients**

**Gap: Clinicians may not be accurately identifying inflammatory skin diseases in children and may not be treating these conditions appropriately.**

*Learning objectives:*

* *Describe the differences in inflammatory skin conditions between adult and pediatric patients.*
* *Compare and contrast strategies for managing inflammatory skin disorders in children and adolescents vs those used in adults.*

A common – and appropriate – maxim in medicine holds that “Children are not small adults.” The manifestations of inflammatory dermatologic conditions may be very different in pediatric patients compared to those seen in adults. The symptoms can be distressing, not just to the child with the disease but to their caregivers as well. Finally, treatment is often empirical, since many drugs approved for adults do not have indications for their use in younger individuals.

The major inflammatory dermatologic disorders in children include atopic dermatitis, psoriasis, erythema multiforme, and lichen planus. (Another related condition, granuloma gluteale infantum, is extremely rare; only about 30 cases have been reported worldwide).[Schwartz]

*Atopic dermatitis* in the United States hasa prevalence among children of 10%-12%, more than 10 times the rate among adults; 85% of these cases occur in the first year of life, and 95% occur by age 5 years. Diagnostic criteria include pruritus, eczematous changes that vary with age, early age of onset, atopy, xerosis, personal history of asthma or hay fever, or history of atopic disease in a first-degree relative in patients younger than 4 years of age. Itch is often the most bothersome symptom; other physical findings include xerosis, lichenification, eczematous lesions, excoriations, and crusting. In infancy, the whole body, except the diaper area, may be xerotic. Early lesions affect the creases with erythema and exudation, later localizing to cheeks, forehead, and scalp. It also involves the extensor surfaces of the legs. These lesions are ill-defined, erythematous, and scaly patches and plaques that are often crusted. Lichenification is rare in infancy.[Schwartz]

In childhood, xerosis continues to be generalized, with lichenification being common over folds, bony protuberances, and the forehead. Lesions are eczematous and exudative. There is often pallor of the face with erythema and scaling around the eyes. Lesions also affect the flexural creases, concentrated primarily in the antecubital and popliteal fossae and buttock-thigh creases. Excoriations and crusting are also common. Clinicians must be careful not to confuse crusting with infection.[Schwartz]

Atopic dermatitis is indistinguishable from other causes of dermatitis. Laboratory testing is rarely necessary, but a platelet count will help exclude Wiskott-Aldrich syndrome. Treatment involves conservative management with lukewarm baths and moisturizers as well as topical steroids. Immunomodulators can be used for resistant lesions. Avoiding triggers (eg, foods that provoke allergic reactions and activities that cause excessive sweating) is important.

*Psoriasis* is a chronic inflammatory disorder for which patients have a genetic predisposition. Psoriasis affects 2%-3% of people in the United States and worldwide, with 10%-15% of new cases beginning before age 10 years.[Schwartz]

Given the lack of officially approved therapies, the very limited evidence-based data from randomized controlled trials, and the absence of standardized guidelines, to date, pediatric psoriasis treatment is primarily based on published case reports, case series, guidelines for adult psoriasis, expert opinions and experience with these drugs in other pediatric disorders coming from the disciplines of rheumatology, gastroenterology, and oncology.[Napolitano]

Restoration of barrier function is key to the successful treatment of psoriasis. Strategies include daily application of moisturizing cream; use of nonprescription tar preparations; sunlight exposure; and oatmeal baths. Salicylic acid may be used to remove large scales. Topical corticosteroids reduce plaque formation and are the first line of therapy along with triamcinolone cream. Vitamin D analogs are used in patients with resistant psoriasis.[Schwartz]

Topical treatment options for pediatric psoriasis include calcipotriene (synthetic vitamin D3 analog), tazarotene (vitamin A derivative [retinoid]; anthralin, corticosteroids, and coal tar (anti-inflammatory and antiproliferative effects); salicylic acid (keratolytic); and calcineurin inhibitors (immune modulators).[Eichenfield] In a recent systematic review of topical therapies in pediatric psoriasis, corticosteroids achieved clearance in 72.7% of patients.[Kravvas] Pediatric psoriasis is a common and challenging condition with no easy and definitive solution. Topical agents are safe, easy to use, readily available and cheap. However, they need to be applied repeatedly, may cause skin irritation, and can be messy. In most cases, all the available topical options should be used before escalating to systemic treatments.[Schwartz] Phototherapy and systemic medications are usually reserved for extensive or refractory disease.[Eichenfield] Methotrexate, cyclosporine, and acitretin are the most commonly used (off-label) conventional systemic agents in both children and adults for the treatment of moderate to severe plaque psoriasis.[Eichenfield] Among biologic agents, etanercept – an anti-TNF agent – has been approved for use in children aged 4 years and older with moderate to severe plaque psoriasis. Anecdotal evidence supports the use of other TNF inhibitors and the IL-12/23 inhibitor ustekinumab. Anti– IL-17 agents may one day play an important role in therapy for children.[Eichenfield]

Clinicians would benefit from education that emphasizes knowledge of how the pediatric psoriasis treatment paradigm is shifting. Recognition of extracutaneous comorbidities and the potential for lifelong chronicity and effect supports a potentially more aggressive management plan in a subset of children for whom a “less is more” approach may not be appropriate.[Eichenfield]

*Erythema multiforme (EM*) is an acute, self-limited condition caused by a type IV hypersensitivity reaction to infections and medications. EM minor represents a localized eruption with minimal or no mucosal involvement, while EM major and Stevens-Johnson syndrome (SJS) represent more severe, possibly life-threatening conditions. EM affects young individuals in their second to fourth decade, although it may also develop in children.[Schwartz]

Prodromal symptoms are usually absent or mild in EM minor. Its abrupt onset often occurs within 3 days of nonspecific upper respiratory tract symptoms, starting on the extremities and spreading centripetally. In the major form, 50% of patients experience a prodromal phase that may include fever, discomfort, cough, sore throat, vomiting, chest pain, and diarrhea for 1-14 days before onset of the rash. The major form may include mucosal, conjunctival, and genital involvement. Half the children with EM have history of herpes simplex virus infection, usually preceding EM onset by 3-14 days. Involvement of at least 2 mucosal surfaces is seen in EM major. It is more severe and characterized by hemorrhagic crusting of the lips and ulceration of the nonkeratinized mucosa (shown). Eye involvement is usually mild, while genital lesions may be painful and often consist of hemorrhagic bullae and erosions. Mucosal lesions usually heal without sequelae. EM major is often associated with generalized lymphadenopathy. Mucosal involvement is more severe and extensive in SJS than EM major.

Treatment is mostly symptomatic, with antihistamines, analgesics, local skin care, and mouthwash. In some cases, topical steroids are prescribed. Most courses are uncomplicated. EM minor usually subsides within 2-3 weeks without scarring. EM major has a mortality rate of less than 5%, with a more protracted course. Hyperpigmentation or hypopigmentation may be noted after healing. Healing of mucosal lesions is usually complete.[Schwartz]

*Lichen planus* is a pruritic eruption that is characterized by violaceous polygonal papules and occasional a fine scale. It mostly affects individuals aged 30-60 years, although it can occur at any age, including childhood. The lesions of lichen planus may present in many clinical forms and are most commonly found on flexor surfaces of the upper extremities, genitalia, and mucous membranes. Maximal spreading occurs in 2-16 weeks. Pruritus is common.[Schwartz] In more than 50% of patients, lesions resolve within 6 months, with 85% resolving within 18 months. The diagnosis is typically clinical, especially in classic cases with flexural involvement. Direct immunofluorescence reveals globular deposits of IgM and complement mixed with apoptotic keratinocytes. Mild cases can be treated with topical steroids; more severe lichen planus may need intensive therapy with retinoids or immunosuppressants.

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**Moles and Melanoma**

**Gap: Increasing rates of advanced disease demonstrate the need for earlier suspicion and diagnosis of melanoma across all age groups and socioeconomic statuses.**

*Learning objective: Distinguish malignant from nonmalignant suspicious neoplasms.*

Melanoma is a neoplasm of melanocytes or a neoplasm of the cells that develop from melanocytes. The incidence of new melanoma cases increases by 1.4% yearly, an annual increase second only to lung cancer in women. According to the American Cancer Society, in 2016, an estimated 78,380 new cases of melanoma will develop, causing 10,130 deaths; about 60% of these cases will be in males. Melanoma is more than 20 times more common in whites compared to African Americans. Overall, the lifetime risk of getting melanoma is about 2.5% (1 in 40) for whites, 0.1% (1 in 1000) for blacks, and 0.5% (1 in 200) for Hispanics.[American Cancer Society] Risk increases with age, with an average age of 63 at diagnosis, but melanoma is one of the most common skin cancers in patients, especially women, younger than 30.[American Cancer Society 2017] Although melanoma accounts for only 1% of skin cancers, it causes a large proportion of skin cancer deaths. However, there are no current formal guidelines from either the US Preventive Services Task Force (USPSTF) or the American Cancer Society regarding screening for melanoma.[ACS 2017; USPSTF 2009]

The incidence of melanoma is rising, according to a recent study of California populations. A new analysis in non-Hispanic whites suggests that rising melanoma rates are real, not attributable to increased levels of detection, and that the burden of the disease could rise significantly in the coming years.[Clarke] Researchers tracked incidence and stage at diagnosis of melanoma across different socioeconomic status (SES) groups. Across all groups, the researchers found increases not only in incidence, but also in advanced disease. Overall, the incidence rose 25% in men from 1998-2002 to 2008-2012 (an average annual age-adjusted incidence of 34.7 to 43.5 per 100,000 person-years), and by 21% in women between those two time periods (from 21.7 to 26.2 per 100,000). Melanoma incidence rate ratios (IRR) increased across all SES classes: by 27% among men in the highest SES neighborhoods, and by 12% among men in the lowest SES neighborhoods. For women, the rates increased by 28% and 13% respectively. The highest increases in the incidence of regional and distant disease occurred in the lowest SES neighborhoods. Researchers noted the importance of not only prevention but developing methods to enhance early detection, particularly in areas where access to providers is limited.[Clarke 2017]

Melanoma is highly curable when detected early, but advanced melanoma spreads to the lymph nodes and internal organs, resulting in death. On average, one American dies from melanoma every hour.

Melanoma has no unique clinical presentation, as it varies depending upon the anatomic location and histopathological type: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma.[Situm 2014] Differential diagnosis include a wide range of benign and malignant skin tumors. Initial observation includes the ABCDE rule (Asymmetry, irregular Border, multiple/unusual Color, large Diameter, evidence mole is Evolving). A dysplastic nevus (also called an atypical or Clark’s nevus is an acquired mole with a unique clinical and histopathologic appearance which sets it apart from the common nevus. These moles appear atypical clinically, often with a “fried-egg” appearance, and are commonly biopsied by providers due to the concern for melanoma. A clinical diagnosis of atypical nevi is based upon the presence of at least 3 of the following features: diameter greater than 5 mm, ill-defined borders, irregular margins, and lesional color variation. Individuals with these nevi have an increased risk for melanoma.[Baigrie 2018]

Identifying new or changing melanocytic lesions, particularly in patients with numerous or atypical nevi, can be challenging.[Berk-Krauss 2017] Dermascopy can be a valuable aid in the detection (augmented by biopsy and histopathological analysis), but clinician experience and education are crucial in optimizing the use of dermascopy.[Situm 2014]  Total-body photography and sequential digital dermoscopy imaging, together known as digital follow-up, are 2 prominent forms of noninvasive imaging technology used in mole mapping that have been found to improve diagnostic accuracy, detect earlier-stage melanomas, and reduce costs.[Berk-Krauss 2017] Clinicians would benefit from education and training aimed at improving the detection and evaluation of suspicious melanocytic lesions.

**Gap: Clinicians who treat skin diseases need more information about the various treatment approaches that are used for melanoma, including newer forms of immunotherapy and targeted therapy.**

*Learning objective: Design a management plan for melanomas at all stages of development.*

Surgery is the definitive treatment for early-stage melanoma, with medical management generally reserved for adjuvant treatment of advanced melanoma. Until 2011, the FDA had only approved two therapies for metastatic melanoma: dacarbazine and high-dose interleukin-2. Adjunctive radiation therapy may be recommended in late stage disease. Since 2011, there have been 8 new approved chemotherapies for advanced melanoma in the US, including ipilumumab, peginterferon alfa-2b, vemurafenib, dabrafenib, trametinib, pembrolizumab, nivolumab, and talimogene laherparepvec, as well as combination dabrafenib with trametinib and nivolumab with ipilumumab. Ipilimumab at the high dose of 10 mg/kg produced a significant improvement in relapse-free survival and overall survival for stage III melanoma patients, but this approach poses a high risk for immune-related toxicities.[Napolitano 2018] New avenues include pathway targeted therapies and immunotherapies. Current immunotherapy approaches include immune checkpoint blockade, interferons, interleukins, combination immunotherapy, and T-VEC vaccine (oncolytic virus therapy).[AIM Foundation]

The discovery that up to 60% of all melanoma tumors have a genetic mutation that causes the amplification of BRAF – a signaling molecule that causes cellular proliferation by the tumor – has led to the approval of selective BRAF enzyme inhibitor that causes programmed cell death in tumors with this mutation. Ipilimumab – one of a new class of agents known as immune checkpoint inhibitors – is a human monoclonal antibody that blocks the activity of CTLA-4 as a down-regulator of T-cell activation. It is approved for the treatment of unresectable or metastatic melanoma based on results of two prospective, randomized, international trials, one each in previously untreated and in treated patients. Vemurafenib is an orally available, small molecule, selective BRAF inhibitor that is approved by the FDA for patients who have unresectable or metastatic melanoma and who test positive for the *BRAF* V600E mutation. Treatment with vemurafenib is discouraged in wild-type BRAF melanoma because data from preclinical models has demonstrated that BRAF inhibitors can enhance rather than downregulate the mitogen-activated protein kinase (MAPK) pathway in tumor cells with wild-type *BRAF* and upstream *RAS* mutations. In May of 2013, two more drugs that target mutations on the BRAF gene were approved: dabrafenib, a BRAF inhibitor and trametinib, a MEK inhibitor. These two inhibitors were then approved in January 2014 as the first approved combination of oral targeted therapies for unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations.

In September 2014, pembrolizumab became the first anti-programmed death (PD-1) antibody to be approved in the United States. PD-1 protein, a T-cell co-inhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumor cells to evade the host’s immune system. Blockade of interactions between PD-1 and PD-L1 enhances immune function in vitro and mediates antitumor activity in preclinical models. The anti-PD-1 and anti-PD-L1 antibodies potentiate immune responses by blocking the interaction between the PD-1 protein, a T-cell co-inhibitory receptor, and one of its ligands, PD-L1—critical players in the ability of tumor cells to evade the host’s immune system. In December 2014, the FDA granted accelerated approval for nivolumab, another PD-L1 inhibitor.

In October 2015 the two-pronged immunological strategy pairing the anti-PD-1 antibody nivolumab with ipilimumab was approved. Several other promising therapies are in various clinical trial stages, including another combination therapy of cobimetinib plus vemurafenib. Oncolytic virus immunotherapy is a new approach that uses native or attenuated live viruses to selectively kill melanoma cells and induce systemic tumor-specific immune responses. A new therapy in this class, talimogene laherparepvec (T-VEC), which is injected directly into melanoma tumors, is a genetically modified version of herpes simplex virus that replicates only in cancer cells, thus destroying tumors while sparing healthy tissues.

Experimental immunotherapy approaches include inhibitory checkpoint molecules (PD-L1, TIM-3, LAG3, and IDO), stimulatory checkpoint molecules (CD40, 4-1BB, KIR, GITR), as well as adoptive T-cell therapy (ACT). Vaccines against melanoma, incorporating killed melanoma cells that trigger the body’s immune response, are also being evaluated in clinical trials; results to date have been mixed. Another emerging immunotherapy approach involves a combination of chemotherapy and radiation, followed by tumor-infiltrating lymphocytes; early evidence suggests this technique can shrink melanoma tumors and prolong life. An even more complex approach involves modifying certain genes within the lymphocytes before administering them to patients. Combinations of these immunotherapeutic strategies are also being investigated.

Certain melanomas – typically those involving the palm of the hand or sole of the foot – involve changes in the C-KIT gene. Clinical trials are underway using drugs such as imatinib, dasatinib, and nilotinib, which are known to target cells with changes in C-KIT. Other studies are investigating drugs that target still other abnormal genes or proteins, such as axitinib, pazopanib, and everolimus.

Given these fast-evolving new therapeutic approaches, and given that many other approaches to the treatment of melanoma are under investigation, clinicians need to stay current about clinical trial updates and emerging therapy options.  As the results from clinical trials mature in the next years, a change in the landscape of adjuvant treatment for melanoma is expected, resulting in new challenges in treatment decisions such as optimizing patients' selection through predictive and prognostic biomarkers, and management of treatment related adverse events, in particular immune-related toxicities.[Napolitano 2018]

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**Onychomycosis and Tinea**

**Gap: Because some clinicians regard onychomycosis as merely a cosmetic problem with little clinical impact, the condition is often untreated or undertreated.**

*Learning objective: Describe the features, the clinical impact, and key steps in the diagnosis of onychomycosis.*

Onychomycosis – the most common nail disorder seen in clinical practice, accounting for about half of such cases – is a fungal nail infection caused by dermatophytes, non-dermatophytes, or yeast.[Lipner 2018a] *Trichophyton* species are the most frequent cause of onychomycosis.[Bodman 2017]

In recent years onychomycosis has increasingly been recognized as a potentially serious medical problem, not merely a cosmetic issue, that can substantially affect quality of life and may lead to risk of complications in patients with comorbid conditions such as diabetes, HIV, and peripheral vascular disease. Onychomycosis may significantly affect a patient’s quality of life by causing local pain and paresthesias and by impairing social interactions.[Lipner 2018a] Onychomycosis is highly prevalent, particularly among older men and patients with compromised distal circulation, nail dystrophies, and/or tinea pedis.[Merck Manual] Based on surveys of adults seeking treatment, the estimated incidence of onychomycosis in the United States and Canada is 8% to 14%, with higher prevalence in older age groups.[Zane 2016]

A yearly, full-body examination that includes fingernails and toenails is the standard of care in dermatology practices, so signs of a fungal infection are likely to be noted, regardless of whether a patient states a concern. The disease is 10 times more common on the feet than hands. Nail fungus on the feet may be missed in the absence of a specific patient complaint, since routine office visits usually do not involve removal of footwear (unless the patient has diabetes). Thus, there is a need for greater attention to examination of the nails during clinical encounters. Differentiation from psoriasis or lichen planus is important because the therapies differ, so diagnosis is typically confirmed by microscopic examination and, unless microscopic findings are conclusive, culture of scrapings or rarely PCR of clippings.[Merck Manual]

Of note, fungal infection of the nails is an increasingly recognized disease in infants and children, one that may be difficult to distinguish from other nail dystrophies but that should always be considered in the differential diagnosis of nail plate disorders.[Eichenfield 2017] Because many clinicians mistakenly believe that onychomycosis does not occur in childhood, the condition is underrecognized and undertreated in the pediatric population.[Eichenfield 2017] Because children’s nails are thinner and faster-growing, they may respond more readily to topical monotherapy than do adults and thus may be good candidates for this approach, although evidence supporting this strategy is scarce. [Eichenfield 2017]

**GAP: Clinicians must become more knowledgeable about the importance of using current treatment options for treatment of onychomycosis, including side effects, drug interactions, and cautions, particularly when treating onychomycosis patients with comorbid diseases.**

*Learning objective: Compare and contrast the safety and efficacy of onychomycosis treatments, including drug interactions and warnings regarding therapy in patients with comorbid disease or receiving other medications.*

Because the toenail acts as a barrier to exogenous substances, its physiological features can hamper drug penetration, making onychomycosis treatment a challenge.[Angelo] Treatment options currently approved in the United States for onychomycosis include topical and oral agents, as well as less common methods including laser therapy, photodynamic therapy, and, in severe cases, surgery.[Goldstein + Bhatia 2018]

Two recently approved topical treatments for nail fungal infections, tavaborole and efinaconazole, are more effective than previous topical therapies, but both must be used for 48 weeks.[Rudd, Family Practice News 2016] In phase 3 studies of efinaconazole, mycologic cure rates were significantly greater with efinaconazole (53.4%-55.2%) compared with the drug vehicle (*P*<0.001).[Tosti, Medscape 2017] A recent study found that the patients who were more likely to achieve complete cure of onychomycosis with efinaconazole at 24 weeks were younger females who had recent disease and who had faster-growing, shorter nails.[Elewski]

In phase 3 studies of tavaborole, mycological cure was reached in 31.1% and 35.9% for active treatment versus 7.2% and 12.2% for the vehicle.[Tosti 2017] Fluconazole and the new triazole agent posaconazole(neither yet approved by the FDA for treatment of onychomycosis) offer an alternative to itraconazole and terbinafine. The efficacy of the newer antifungal agents lies in their ability to penetrate the nail plate within days of starting therapy.[Tosti 2017] The topical imidazole molecule luliconazole for onychomycosis of the great toenail has shown promising results in clinical trials.[Watanabe 2017] Clinical cure rates up to 88% at 4 weeks post treatment have been reported.[Khanna 2014] Other topical antifungals are being evaluated in the US and abroad. Several laser devices have been used to treat onychomycosis, including Nd:YAG lasers and diode lasers. Laser treatment can be combined with topical antifungals.[Tosti]

Because antifungals are potent medications that carry a number of cautions, the American Academy of Dermatology (AAD) in 2013 released recommendations that advise clinicians to "Choose Wisely": "Approximately half of nails with suspected fungus do not have a fungal infection. As other nail conditions, such as nail dystrophies, may look similar in appearance, it is important to ensure accurate diagnosis of nail disease before beginning treatment. By confirming a fungal infection, patients are not inappropriately at risk for the side effects of antifungal therapy, and nail disease is correctly treated."[AAD Guideline 2013]

*Agents Approved for the Treatment of Onychomycosis*

|  |  |  |
| --- | --- | --- |
| **Antifungal Agent** | **Drug Class** | **Indication** |
| **Oral** |  |  |
| Itraconazole | Triazole antifungal | Onychomycosis due to dermatophytes (tinea unuium) |
| Terbinafine | Allylamine antifungal | Onychomycosis due to dermatophytes (tinea unuium) |
| **Topical**  |  |  |
| Ciclopirox | Synthetic hydroxypyridone derivative | Mild-moderate onychomycosis of nails without lunula involvement due to *T. rubrum* |
| Efinaconazole | Triazole antifungal | Onychomycosis of toenails due to *T. rubrum* and *T. mentagrophytes* |
| Tavaborole | Boron-based antifungal | Onychomycosis of toenails due to *T. rubrum* and *T. mentagrophytes* |

*Source: Goldstein + Bhatia 2018*

Oral agents must be chosen for their activity against the involved pathogens (dermatophytes, nondermatophytes, or yeast species, or combination infections). The currently approved agents are generally safe for most patients, but concerns remain with respect to systemic side effects (for example, hepatotoxicity), particularly in pediatric patients, the elderly, and patients with underlying medical conditions such as diabetes. Clinicians should also be aware of the numerous drug-drug interactions with oral agents that are metabolized by the CYP system.[Zane 2016] Furthermore, clinicians should be aware that, in addition to relatively low cure rates, relapse rates can be as high as 50%.[Angelo]

Several agents are in development for the treatment of onychomycosis. A class known as echinocandins (including anidulafungin, caspofungin, and micafungin) has shown strong in-vitro activity against dermatophytes.[Sahni] An investigational antifungal agent, ME1111, acts primarily through the inhibition of an enzyme involved in the electron transport chain in mitochondria and potentially offers a combination of valuable characteristics: potent antidermatophyte activity, low molecular weight leading to increased penetration, and good inhibitory activity even in the presence of keratin.[Sahni]

As noted, clinicians may underestimate the impact of onychomycosis on their patients. In today’s health care environment, management organizations are implementing initiatives designed to improve patient satisfaction, some of which may include the use of validated patient-reported outcome (PRO) measures such as OnyCOE-t, to evaluate treatment response.[Wang 2017] Given the availability of new agents for treating onychomycosis, PROs will be increasingly important in onychomycosis to assess patient priorities and optimize treatment.[Wang 2017] Clinicians must be able to effectively and safely use the currently approved agents and must be prepared to evaluate the emerging data on medications now being investigated.

**Gap: While tinea is a common condition, and is usually not serious, it can cause discomfort and is highly contagious.**

*Learning objective: Design effective therapy targeted to address the different forms of tinea.*

Tinea is the broad term for infection caused by dermatophytes. Tinea pedis (“athlete’s foot”) is the most common form. Symptoms include itching, stinging, and burning between the toes and on the soles of the feet; blistered, cracked, or peeling skin, and discolored or thickened toenails. Other types affect the nails (tinea unguium, also called dermatophyte onychomycosis), the groin (tinea cruris), the scalp (tinea capitis), and other sites on the body. It is possible for tinea infections to occur at multiple sites simultaneously.[Goldstein + Goldstein 2018]

In most cases diagnosis is made on the basis of clinical findings. However, because other cutaneous disorders share features in common with tinea, testing is recommended to confirm the diagnosis. Options include use of a potassium hydroxide preparation or a fungal culture. If the patient exhibits significant erosions, ulcerations, or malodor, a Gram stain may be needed to identify a secondary bacterial infection. Newer techniques such as polymerase chain reaction and mass spectroscopy can identify different dermatophyte strains involved. Clinicians need to be able to differentiate tinea from other potential infections, because inappropriate treatment with steroids, for example, may alter the appearance of the infection and make diagnosis more difficult. The differential diagnosis includes interdigital tinea pedis, hyperkeratotic (moccasin-type) tinea pedis, and vesiculobullous (inflammatory) tinea pedis.

Tinea should be treated, both to provide relief to the patient and to prevent the spread of infection. Several options are available for treating tinea. Most superficial cases are managed with topical therapies such as allyamines, azoles, butenafine, ciclopirox, and tolnaftate. Oral agents such as griseofulvin, fluconazole, itraconazole, and terbinafine are indicated for extensive or refractory infections in patients for whom topical therapy is ineffective. Clinicians need to be aware that some agents should not be used. For example, oral ketaconazole poses a risk for severe liver injury, adrenal insufficiency, and drug interactions, and nystatin, while effective for *Candida* infections, is not effective against dermatophytes.

Investigational agents for tinea include BB2603, a squalene epoxidase inhibitor in spray form; and SB208, a cell-death stimulant in gel form for interdigital tinea pedis.[Sahni]

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**Pathophysiology of Dermatologic Diseases**

**Gap: Clinicians may not recognize the need for, or the techniques used in, assessing the immune status of their patient subtypes so as to select appropriate therapy.**

*Learning objective: Design personalized management strategies that identify and address the specific immunological derangements found in patients with various dermatological conditions.*

Basic science continues to unveil the physiological mechanisms that underlie diseases of the skin and that trigger characteristic immunological and inflammatory signs and symptoms. Such findings are critical for understanding the nature of these conditions and for developing new targeted therapies that hold promise for better outcomes. Two key components of the immune system with significant implications in dermatology are eosinophils and immunoglobulin E (IgE).

Eosinophils are proinflammatory white blood cells packed with large granules that contain various proteins and enzymes. The presence of eosinophils in tissues or peripheral blood is associated with many noncommunicable allergic and inflammatory skin diseases, including psoriasis and atopic dermatitis.[Eyerich; Khoury] Recent advances in lymphocyte immunology and molecular genetics are illuminating the complex interactions between eosinophils and other components of the immune system that result in at least 6 known distinct symptom patterns.[Eyerich] To cite just one example: The psoriatic pattern is mediated by type 3 lymphocytes, including Th17, Tc17, ILC3, and Th22 cells.[Eyerich] Awareness of these emerging patterns holds more than just scientific interest; it is highly clinically relevant.[Eyerich] Such information is being used to develop diagnostic criteria, to establish techniques for acquiring and assessing biopsy samples, and to establish biomarkers for use in clinical trials and in assessing treatment outcomes.[Khoury] Importantly, identifying the presence of high levels of eosinophils (such as in certain types of severe asthma) has led to the developed of therapies targeting this specific pattern.

Similarly, elevated levels of IgE are seen in various allergic and dermatologic conditions. High IgE levels are a hallmark of atopic dermatitis, found in 80% of patients with the disease.[Kasperkiewicz]. Omalizumab, an anti-IgE monoclonal antibody, was approved for treatment of moderate to severe persistent asthma and was also approved for use in chronic idiopathic urticaria (hives without a known cause).[Radonjic-Hoesli] A therapeutic technique known as immunoadsorption has been successfully used as a treatment for IgE autoantibody-mediated diseases such as pemphigus; experts are now applying the method to patients with severe atopic dermatitis and high IgE levels.[Kasperkiewicz]

Clinicians would gain from knowledge of the role these immune components play in dermatologic disease. Further, they would benefit from a greater understanding of how to use information about these immunological patterns to classify their patients and develop personalized therapeutic strategies to improve outcomes.

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**Photodermatoses**

**Gap: Clinicians often fail to differentiate light-related skin disorders (photodermatoses) from other dermatologic conditions and thus may provide erroneous or ineffective management.**

*Learning objective: Differentiate the various photodermatoses from other dermatologic conditions whose symptoms manifest in similar ways.*

Photodermatoses are skin conditions that result from an abnormal reaction to sunlight, most often to the ultraviolet component (UVA/UVB), but also to visible light.[Lehmann; Nahhas] Photodermatoses – which can be broadly classified as immunologically mediated, chemical- and drug-induced, photoaggravated, and inherited (genetic) – include polymorphous light eruption, actinic prurigo, hydroa vacciniforme, chronic actinic dermatitis, erythropoietic protoporphyria, SLOS, xeroderma pigmentosum, Cockayne syndrome, UV-sensitive syndrome, trichothiodystrophy, Bloom syndrome, Rothmund-Thomson syndrome, and Kindler syndrome.[Nahhas] Such disorders are usually not life-threatening in themselves, but they can significantly diminish a patient’s quality of life. Furthermore, they may increase a patient’s risk for complications, including malignancy.

Clinicians are often challenged to identify light-related skin disorders because of the significant overlap between their symptoms and those of other dermatologic conditions. Accurate diagnosis requires a detailed history, a thorough physical exam, and appropriate laboratory testing.[Nahhas] Consideration should also be given to a patient’s ethnicity, since the epidemiology and presentation of a photodermatitis varies widely among different racial and ethnic populations (ie, skin of color).[Gutierrez] Among the conditions that must be considered in the differential diagnosis are systemic lupus erythematosus, contact dermatitis, atopic dermatitis herpes infections, and adverse reactions to drugs. Conducting a complete evaluation can be complicated and may involve phototesting, provocative phototesting, and photopatch testing.[Nahhas] Patients may need to be counseled about temporarily suspending use of certain therapies, such as systemic immunosuppression or antihistamines, which might affect results. Clinicians would benefit from greater knowledge of available diagnostic and management strategies.

Use of adequate sun protection is a crucial for preventing photodermatoses or for managing them once they occur. However, many people do not know about effective steps for prevention or they do not apply preventive techniques adequately. In a recent study, free sunscreen was provided to attendees at a state fair.[Wood] Observers reported that two-thirds of these subjects failed to apply sunscreen appropriately to all areas of exposed skin. Nearly 40% did not take additional protective measures, such as wearing a hat, sunglasses, or long-sleeved apparel. Reflecting the common misbelief that cloud cover obviates the need for protection, sunscreen use decreased dramatically on overcast days.[Wood] Clinicians would benefit from training on how to counsel patients about effective protective strategies.

**Gap: Clinicians do not always provide their patients with appropriate counseling about effective strategies for protecting against sun exposure to reduce the risk for skin cancers and to prevent premature skin aging.**

*Learning objective: Discuss photoprotection with patients, including pediatric patients and their caregivers.*

The greatest degree of sun exposure occurs through adolescence.[Andreola 2018] Proper and consistent photoprotection can minimize the risk of photocarcinogenesis. Effective techniques include shade seeking, the use of physical agents (clothing, sunglasses, hats) to protect against ultraviolet radiation (UVR) exposure, and the proper application and re-application of sunscreens on all exposed areas.[Cestari 2017] Avoiding use of tanning beds is an important consideration for adolescents.[Cestari 2017]

Parents are generally responsible for instituting appropriate sun protection in younger children, while adolescents become responsible for their own photoprotective behaviors. Evidence demonstrates that, although adolescents are aware of the risks of sun exposure, they do not consistently use effective sun protective measures.[Andreola 2018] Further, adolescents may be more likely to get their information about the importance and means of sun protection from their parents, and not from their pediatrician or primary care clinician.[Andreola 2018]

Use of adequate sun protection is a crucial for preventing photodermatoses or for managing them once they occur. However, many people do not know about effective steps for prevention or they do not apply preventive techniques adequately. In a recent study, free sunscreen was provided to attendees at a state fair.[Wood] Observers reported that two-thirds of these subjects failed to apply sunscreen appropriately to all areas of exposed skin. Nearly 40% did not take additional protective measures, such as wearing a hat, sunglasses, or long-sleeved apparel. Reflecting the common misbelief that cloud cover obviates the need for protection, sunscreen use decreased dramatically on overcast days.[Wood] Clinicians would benefit from training on how to counsel patients about effective protective strategies. Notably, only one-third of those observed properly applied sunscreen over all of their exposed skin; further, sunscreen use substantially dropped on cloudy days, even though up to 80% of UV rays can penetrate the clouds. Adults who are not aware of effective sun-protection strategies or who do not use them properly for themselves will likely not provide proper guidance for their children.

Emerging evidence suggests that that individuals who have had previous nonmelanoma skin cancer (NMSC) have higher rates of use of shade, long sleeves, hats, and sunscreen compared with individuals without a history of NMSC. However, both groups were shown to have comparable rates of recent sunburn, indicating the need for continued education, particularly among younger adults, for sunburn prevention and sun avoidance.[Fischer 2016]

Clinicians must impart appropriate education to patients of all skin colors. A study in the UK found that lighter-skinned adolescents had greater use of sunscreen than darker-skinned adolescents.[Gould 2015] In addition, adolescents are less likely to routinely use sunscreen; 44% of adolescents reported never wearing sunscreen while at home during the summer, compared with 1% who used sunscreen when on holiday. The study suggests adolescents with fairer skin are more likely to be aware of the need to protect their skin compared with those whose skin tone is darker. Adults with skin of color are less likely to be diagnosed with melanoma; however, when they do develop melanoma, it is often at a later stage of disease than in lighter-skinned adults.[Barsh 2003; Baumann 2016]

Vitamin D – predominantly obtained via sun exposure – plays an important role in skeletal health in both young and elderly persons. Persons who do receive sufficient vitamin D from sun exposure need supplemental oral intake to prevent rickets and to minimize risk of developing osteoporosis later in life.[Kannan 2014] This may affect children with photosensitivity disorders owing to underlying systemic diseases. Pediatricians may need to work with dermatologists to diagnose and manage a photodermatosis in pediatric patients.[Chantom 2012]

Clinicians should be prepared to counsel patients about the importance of sun protection to minimize risk for skin cancer while ensuring that their vitamin D intake is sufficient to promote skeletal health.

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**Psoriasis**

**Gap: Because many clinicians have a poor understanding of psoriasis as a systemic, immune-mediated disease with multiple comorbidities, psoriasis is often underdiagnosed and undertreated.**

*Learning objective: Explain the pathophysiological mechanisms that underlie psoriasis and its comorbidities.*

Psoriasis is an inflammatory chronic, immune-mediated systemic disease affecting 3.2% of the adult US population (approximately 8 million people). Characterized by pruritic inflammatory plaques with a chronic remitting and relapsing disease course, psoriasis is associated with significant comorbidities including obesity, metabolic syndrome, cardiovascular disease, psoriatic arthritis, autoimmune disease, psychiatric illness, liver disease, smoking, malignancy, chronic obstructive pulmonary disease, sleep apnea, and alcohol abuse, resulting in a markedly decreased quality of life.[Menter A, AAD agenda, July 2017] Psoriatic arthritis develops in 10%-30% of these patients approximately 10 years after the onset of skin disease.[ [MAPP 2016; Mease et al 2014; Young 2017] Insight into the overlapping pathogenesis of psoriasis comorbidities highlights the importance of immune-mediated mechanisms in these disease states.[Menter, AAD 2017; NPF Guidelines 2016; Eissing 2015]

Clinicians may lack a thorough understanding of psoriasis beyond its dermatologic manifestations. For example, in a recent survey, 75% of dermatologists and rheumatologists acknowledged that psoriatic arthritis may be underdiagnosed because of a failure to connect skin and joint symptoms. Fewer than half of primary care physicians reported screening psoriasis patients for cardiovascular risk factors, as recommended by National Psoriasis Foundation guidelines[Parsi]. Thus, accurate diagnosis and effective management of psoriasis and its comorbidities requires a deeper understanding of its pathophysiology.

**Gap: Many clinicians fail to apply updated treat-to-target guidelines for diagnosis, treatment, and assessment of progress in patients with psoriasis, who often remain undertreated or unsatisfied with treatment.**

*Learning objective: Describe optimal strategies for applying current clinical guidelines in the diagnosis and management of psoriasis.*

In a recent survey of dermatologists, 92% acknowledged that the disease burden of psoriasis is frequently underestimated and that the condition is undertreated.[van de Kerkhof, MAPP 2015] Among patients with psoriasis, 24%-35% of those with moderate psoriasis, and 9%-30% with severe psoriasis were untreated.[Armstrong, Dermatol Ther 2017] In a 2016 survey, only 1 in 3 patients were satisfied with their treatment plan, and more than 80% reported emotional impacts resulting, in part, from lack of knowledge about what to expect.[Gould 2016] Barriers to guideline adherence frequently cited by physicians include lack of knowledge and fear of side effects, suggesting the need for further educational strategies.[MAPP]

Clinicians also need expanded knowledge and improved clinical confidence in assessing disease severity, treatment results, and quality of life.[Gottlieb 2016] Clinicians should discuss treatment goals with patients, stressing that control of the disease is the primary aim and that remission may be achievable with appropriate use of therapies in appropriately chosen patients. Treatment goals for psoriasis include rapidly controlling the disease process; achieving and maintaining remission; minimizing adverse events; and enhancing quality of life. For mild-to-moderate disease, topical therapies may suffice. Choices include emollients, corticosteroids, vitamin D analogs such as calcipotriene and calcitriol, tar, and topical retinoids (tazarotene). Topical tacrolimus or pimecrolimus are alternatives for use in facial or intertriginous areas. Using different vehicles and combination topical therapies may also be effective. Severe psoriasis (affecting >5%-10% of body surface area) requires phototherapy or systemic therapies such as retinoids, [methotrexate](https://www.uptodate.com/contents/methotrexate-drug-information?source=see_link), [cyclosporine](https://www.uptodate.com/contents/cyclosporine-ciclosporin-drug-information?source=see_link), [apremilast](https://www.uptodate.com/contents/apremilast-drug-information?source=see_link), or biologic immune modifying agents.[Young 2017] Keeping the regimen simple and acceptable to the patient can maximize adherence.

The National Psoriasis Foundation (NPF) suggests that clinicians need to understand and use defined treatment targets, citing clinical assessment tools including changes in BSA (Body Surface Area), Psoriasis Area and Severity Index (PASI), Physician Global Assessment (PGA), and Dermatology Life Quality Index (DLQI).[Armstrong 2017] The treat-to-target strategy allows patients and their health care providers to take better control of psoriatic disease by setting specific targets and goals for improved health outcomes.[NPF Treat to Target, 2017]

Periodic assessments using treatment targets provide a clear evaluation of progress and a guide for adjusting treatments. A recent consensus of experts concluded that an initial goal should be to reduce psoriasis BSA to ≤1% within 3 months of starting treatment; if the goal is not met, an "acceptable response" is 75% improvement in BSA. During the maintenance period, the consensus on the target response was BSA ≤1% at every 6-month assessment interval.[Duffy 2016]

**Gap: Patients with psoriasis may not respond adequately to treatment or they may experience diminished benefit over time. New and emerging treatments show favorable efficacy and safety for psoriasis, but many clinicians fail to understand the role of biologics and may underutilize these therapies.**

*Learning objective: Identify patients with psoriasis who may be appropriate candidates for biological therapy.*

The advent of biologic agents has allowed treatment goals for psoriasis to be more aggressive. These agents also have made remission a potential and realistic goal.[Feldman 2017] Biologic immune- modifying agents act through targeted inhibition of specific cytokines associated with inflammatory immune responses and skin lesions.[Leonardi 2015, Young 2017]

Several biologic agents have been approved for the treatment of psoriasis. Older biologics target TNF-α, while the more recently approved agents target interleukin (IL)-17. In 2017 the FDA approved guselkumab, the first monoclonal antibody that selectively blocks IL-23, for treatment of moderate-to-severe psoriasis. Guselkumab received FDA approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[Janssen press release] A number of other IL-23 antagonists are in late-stage development. A biosimilar was introduced to the US market within the last year, and alternative maintenance regi­mens have been studied.

**Biologics and small molecules approved for psoriasis**

|  |  |  |
| --- | --- | --- |
| **Biologic** | **Target** | **Year Approved for Psoriasis** |
| Adalimumab | TNF-α | 2008 |
| Apremilast | PDE-4 | 2014 |
| Brodalumab | IL-17A | 2017 |
| Etanercept | TNF-α | 2004 |
| Golimumab | TNF-α | 2009 |
| Guselkumab | IL-23 | 2017 |
| Infliximab | TNF-α | 2006 |
| Ixekizumab | IL-17 | 2016 |
| Secukinumab | IL-17A | 2015 |
| Ustekinumab | IL-12/IL-23 p40 | 2009 |

*Source: Blauvelt JAAD 2016; Blauvelt Br J Derm 2017; Reich 2017*

**Table 2: Agents Under Investigation**

|  |  |  |
| --- | --- | --- |
| **Biologic** | **Status** | **Target/Mechanism** |
| **BI 655066** | **Phase 3** | **IL-23** |
| CF101 | Phase 3 | A3 adenosine receptor agonist |
| IMO 8400 | Phase 2 | Antagonist of Toll-like receptors (TLRs) 7, 8 and 9 |
| Namilumab | Phase 2 | Human monoclonal antibody; inhibits granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling by binding the soluble cytokine |
| Neihulizumab | Phase 2 | Preferentially induces apoptosis of late-stage activated T cells, effectively eliminating chronic pathogenic T cells while fully maintaining host defense |
| Risankizumab | Phase 3 | IL-23 |
| Sotrastaurin | Phase 2 | Pan-protein kinase C (PKC) inhibitor; preserves regulatory T cells and prevents IL-17 production. |
| Tildrakizumab | Phase 3 | IL-23 |
| Tregalizumab | Phase 2 | Humanized anti-CD4 monoclonal antibody; induces selective activation of regulatory T-cells |

*Source: Hilton L 2016; Leonardi 2017*

A recent publication suggests that, based on results of studies with newer biologic agents, the current objective criterion of PASI 75 for therapeutic endpoints in clinical trials should be raised to PASI 90 or 100.[Manolo 2015] Clinicians would benefit from education that presents the rationale for more aggressive therapeutic targets and provides information about how best to design therapy to achieve these goals in real-world practice.

Adherence may be significantly better in patients receiving biologic therapies, but costs can be a challenge.[Cheng 2014] Clinicians need to become familiar with patient eligibility for biologics as well as strategies for assisting patients with access and payment.[Gottlieb 2016] Primary care clinicians would benefit from guidance regarding when to refer patients with psoriasis to specialists.[Gottlieb 2016]

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**Public Health and Dermatology**

**Gap: Clinicians need to increase their awareness of effective strategies that can reduce dermatologic conditions on a population basis.**

*Learning objective: Recognize the benefits of community-based preventive strategies aimed at reducing the incidence of skin disease, including cancer.*

The classic definition of public health is “the science and the art of preventing disease, prolonging life, and promoting physical health and mental health and efficiency through organized community efforts toward a sanitary environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and treatment of disease and the development of the social machinery to ensure to every individual in the community a standard of living adequate for the maintenance of health.”[Winslow]

Given that definition, dermatologists are in a unique position to promote skin health by decreasing the burden of skin diseases, reducing health care costs, and improving the overall quality of life of people in the community.[Williams] However, modern public health dermatology is still relatively underdeveloped.[Williams]

The key to effective public health is prevention. One important program in this arena is the Healthy People 2020 initiative.[Healthy People 2020] Among its goals in dermatology are a reduction in the melanoma cancer death rate; a decrease in the proportion of people who report sunburn and who use artificial tanning methods; and an increase in the proportion who use protective measures against skin cancer. Preventing infectious diseases is another main focus of public health efforts.

Evidence suggests that a “low-risk” approach of reducing risk in the whole population for diseases such as melanoma may achieve more than a “high-risk” approach of targeting just those who have skin cancer or who are at higher risk of developing skin cancer.[Williams]

Clinicians should be aware of the tools and resources available to achieve these goals.

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**Rosacea**

**Gap: Many clinicians and patients have a poor grasp of the typology, risk factors, and triggers of rosacea.**

*Learning objective: Design a comprehensive strategy for the management of rosacea.*

Rosacea is a common chronic skin condition of the face that affects approximately 16 million American adults; according to the National Rosacea Society (NRS), only a small fraction of these patients are being treated.[NRS] More than 90 percent of rosacea patients have reported reduced self-confidence and self-esteem, and 41 percent reported avoiding public contact, and 88 percent of those with severe symptoms said the disorder had adversely affected their professional interactions; half of these patients reported missing work because of their condition.[Moustafa 2014; NRS] Nearly half of respondents to another NRS survey had never heard of rosacea prior to receiving their diagnosis, and 95% had known little or nothing about the signs and symptoms of rosacea prior to their diagnosis.

Rosacea is a chronic disorder with intermittent periods of exacerbation. The underlying pathogenesis is unknown. However, major pathogenic components appear to be inflammatory, vascular, and neural in origin.[Wilkin] Histology identifies blood vessel dilation, infiltration of T-helper cells, macrophages, and mast cells. Keratinocyte Toll-like receptors may play a role in the pathogenic process of immune system activation.[Weinkle 2015] A genetic component has been identified in about half the cases.[Aldrich 2015]

**Rosacea Typology**

|  |  |
| --- | --- |
| **Classification of rosacea** | **Description** |
| Erythematotelangiectatic | Central facial erythema (flushing) that can be persistent or transient |
| Papulopustular | Inflamed pustules or papules |
| Phymatous | Skin thickening and nodules on the nose, cheeks, or chin |
| Ocular | Red, itchy, burning, and watery eyes that often co-occur in 20% of patients with other types of rosacea |

*Source: Wick JY, 2016*

Triggers and risk factors may not be clear to patients and often are not clear to clinicians. In a recent survey of clinicians' rosacea knowledge, 90% of respondents were not aware that rosacea is associated with past but not current smoking.[Frontline Medical Communications. MD-IQ quiz. 4/18/2016-8/03/2016] [Li 2017] Many need education about diagnostic signs. For example, 60% failed to identify conjunctival hyperemia as the most commonly reported sign of ocular rosacea.

Physician education and physician/patient communication need to become an important part of the treatment plan for patients with rosacea as well.

**Gap:. Many clinicians lack current, clinically relevant information on traditional, novel, and emerging therapies for rosacea, their mechanisms of action, and their efficacy and safety as monotherapy and in combination treatment regimens**

*Learning objective: Compare and contrast the benefits and risks of current and emerging therapies for rosacea.*

No cure exists for rosacea, but healthcare professionals have several options to treat the symptoms. In this regard, many clinicians could benefit from education to improve their clinical practice. For example, 60% of survey respondents did not know that tetracyclines are the most common antibiotic that is effective in ocular rosacea.[Frontline Medical Communications 2016]

Many topical agents are available. Topical [azelaic acid](file:///F%3A%5Crizzom%5Ctopic%5Cazelaic-acid) may be used to reduce inflammatory lesions, bumps, and papules. Metronidazole, a cornerstone of papulopustular rosacea treatment, seems to have antimicrobial, antioxidant, and anti-inflammatory properties.[Wick 2016] Brimonidine tartrate gel, FDA-approved in 2013 for facial flushing, acts as a vasoconstrictor. In 2014, the FDA approved a topical formulation of ivermectin cream for the treatment of inflammatory lesions related to papulopustular rosacea.[FDA 2014] Azelaic acid in a foam formulation that is effective against papulopapular rosacea, was FDA approved in 2015. Topical oxymetazoline hydrochloride cream, which significantly improves rosacea-associated erythema, was approved by the FDA in 2017. In phase III studies, efficacy of topical oxymetazoline increased over the course of 52 weeks.[McNamara 2017] Minocycline foam, which inhibits numerous bacterial species and inflammation, is currently in phase III trials.[Jesitus 2017]

Oral [tetracycline antibiotics](file:///F%3A%5Crizzom%5Ctopic%5Ctetracycline-antibiotics) and topical antibiotics are often the first line of therapy, prescribed to relieve papules, pustules, and inflammation. If papules and pustules persist, isotretinoin, which reduces sebum production and the size of sebaceous glands, may be considered.[Wick 2016] Doxycyline 40 mg (a sub-antimicrobial dose) may be as effective as monotherapy or used in combination with topical agents.[Wick]

Omiganan pentahydrochloride, under study for papulopustular rosacea, is an aqueous-based topical cationic antimicrobial peptide with rapid bactericidal activity against microorganisms colonizing the skin.[Clinical Trials.gov 2017]

Light therapy such as pulsed dye laser and intense pulsed light can be used for multiple types of rosacea.[Do 2016] In a recent survey, patients given a series of recurring pulse dye laser treatments reported decreasing symptoms and improved quality of life.[Do 2016]

Clinicians must be kept apprised of new data on traditional, novel, and emerging therapies for rosacea, their mechanisms of action, and their efficacy and safety as monotherapy and in combination treatment regimens.

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**Scars and Keloids**

**Gap: Clinicians may not be treating keloids using strategies that avoid scarring.**

*Learning objective: Discuss techniques for managing keloids that offer the greatest benefit with minimal risk of scarring.*

Hypertrophic scars and keloids are aberrant variations of typical wound healing. Keloids, which result from an overgrowth of dense fibrous tissue that develops after healing of a skin injury, involve tissue that extends beyond the borders of the original wound, do not usually regress spontaneously, and tend to recur after excision. Hypertrophic scars are common after thermal injuries and other injuries that involve the deep dermis, and typically do not expand beyond the borders of the original wound. These scars are characterized by erythematous, pruritic, raised fibrous lesions.[Berman]

Standard treatment of hypertrophic scars and keloids comprises occlusive dressings, compression therapy, and intralesional corticosteroid injections, and combinations of these therapies.[Berman] Compression treatments include button compression, pressure earrings, ACE bandages, elastic adhesive bandages, compression wraps, spandex or elastane (Lycra) bandages, and support bandages. Other pressure devices include pressure earrings and pressure-gradient garments made of lightweight porous Dacron, spandex (also known as elastane), bobbinet fabric (usually worn 12-24 hours per day), and zinc oxide adhesive plaster. Overall, 60% of patients treated with these devices showed 75%-100% improvement.[Berman]

Intralesional injection of various agents alone and in combination, including triamcinolone, interferon, 5-fluorouracil, doxorubicin, and bleomycin, have resulted in modest degrees of keloid flattening. Therapies have also included cryosurgery, laser therapy, verapamil, retinoic acid, imiquimod 5% cream, tamoxifen, tacrolimus, botulinum toxin, hydrogel scaffold. Many of these therapies are not yet approved by the FDA.[Berman]

One study reported molecular-based evidence of the clinical benefits of adding 5-fluorouracil to a steroid injection for improved scar regression and reduced recurrence of keloids.[Huang] 5-fluorouracil–induced G2 cell-cycle arrest and apoptosis may be associated with p53 activation and p21 up-regulation. The combination of 5-fluorouracil to triamcinolone significantly affected the treatment, leading to more significant cell proliferation inhibition, apoptosis, Col-1 suppression, and MMP-2 induction [Huang]

In a more recent study, surgical excision combined with intraoperative platelet-rich plasma (PRP) and adjuvant postoperative in-office superficial radiation therapy (SRT) achieved a 94% nonrecurrence rate on follow-up over a 2-year period. Researchers conducted a retrospective analysis of 49 patients treated with extralesional surgical excision of keloids localized to the ear followed by the application of autologous PRP to the wound site and postoperative in-office SRT. Fifty ear keloids were treated with this method in patients aged 15 to 66 years (mean=32, SD=16) of which 14 were male and 35 female.[Jones]

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**Urticaria**

**Gap: Clinicians may be unfamiliar with guidelines that outline the stepwise approach to managing chronic urticaria.**

*Learning objective:* *Implement treatment for urticaria that reflects the severity of the disease and the response to therapy of individual patients.*

Urticaria (commonly known as hives) is a heterogeneous skin disorder whose underlying cause is unknown; it may be acute (<6 weeks’ duration) or chronic (>6 weeks) and is defined by the appearance of wheals with or without angioedema.[Zuberbier] Acute urticaria is usually triggered by exposure to certain food, drugs, or insect bites and may affect up to 20% of the population. Chronic urticaria is less prevalent (~5%) and may result from such underlying conditions as thyroid disease, autoimmune disorders, chronic infections, early malignancies, or physical stimuli.[Zuberbier]

Wheals appear suddenly, producing central swelling and surrounding erythema; they are typically pruritic and resolve within about 24 hours. In the United States, urticaria is classified as continuous or intermittent. Provocation tests can be used to confirm the suspected cause of symptoms. However, extensive routine diagnostic testing without a supporting patient history is not recommended, since results rarely alter the management and treatment of chronic spontaneous urticaria.[Tarbox] A skin biopsy may be needed to differentiate urticaria from other vascular conditions. Acute urticaria should also be distinguished from anaphylaxis, which requires emergency treatment with epinephrine. US guidelines recommend obtaining an objective assessment of itch severity and determining the quantifiable percentage of the body covered in hives each day (ie, a visual analogue scale) to assess the severity of hives and to evaluate response to treatment.[Zuberbier]

Treatment of urticaria is stepwise.[Bernstein] The first step calls for use of second-generation antihistamines, such as loratadine or cetirizine, which carry an indication for urticaria. However, only about half of patients respond to this approach. If response is inadequate, higher doses may be needed, or an additional drug may be added (eg, another second-generation or a first-generation antihistamine; or a leukotriene receptor antagonist). For nonresponsive patients, a potent antihistamine such as doxepin or hydroxyzine may be considered. In severe cases, alternative agents should be tried, including omalizumab or cyclosporine; anti-inflammatory agents; immunosuppressants; or biologics. Omalizumab, an IgE inhibitor, was approved in 2014 and is indicated for the treatment of chronic idiopathic urticaria in people aged 12 years or older who continue to have symptoms despite treatment with antihistamines. It is the first biologic and the first new class of medication to be approved for this condition since the introduction of nonsedating H1-antihistamines in the early 2000s.[Kaplan]

Clinicians would benefit from greater awareness of current guidelines for management of urticaria, and from greater familiarity with older, newer, and emerging agents for use in treating the condition.

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