OVERALL 2018 CONFERENCE NEEDS ASSESSMENT

TABLE OF CONTENTS

Program Overview

The Skin Disease Education Foundation presents the 19th Annual Las Vegas Dermatology Seminar, featuring the 15th Annual Psoriasis Forum, November 1-3, 2018, at which nationally recognized leaders in dermatology come together to discuss and review the current state of knowledge surrounding the diagnosis, treatment, and monitoring of patients with dermatologic diseases. The program features key clinical topics including psoriasis, acne, actinic keratoses, aesthetic dermatology, atopic dermatitis, contact dermatitis, seborrheic keratosis, onychomycosis and tinea, rosacea, clinical cases, and other important issues in medical dermatology.

This activity has been designed to provide a forum for dermatologists and other clinicians including residents, to receive relevant and timely information regarding the most recent developments in the field of dermatology with a special emphasis on psoriasis. The setting was chosen to accommodate the size of the meeting and the length of the educational program. The objective of the meeting is to provide an environment that is conducive to learning – the relaxed environment and the size of the conference provides participants with access to key thought leaders throughout the 3-day period – access that would not normally be readily available. Participants attend the lectures, participate in interactive sessions, view procedures and consult with thought leaders throughout. The outcomes of the conference are positive with many participants returning year after year. This is the 19th year of this conference and the 15th year of the Psoriasis Forum, which is a key component of SDEF's Las Vegas Dermatology Seminar. This highly interactive Psoriasis Forum will be of interest to both the seasoned clinician and residents in training.

This seminar is designed for clinicians with all levels of expertise and experience in dermatology and takes place in an informal and relaxed atmosphere to encourage the exchange of ideas and information.

Learning Objectives

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

- Develop a comprehensive treatment plan for acne patients based on clinical guidelines, incorporating pharmacologic and nonpharmacologic strategies.
- Integrate into clinical practice the most recent research on the etiologies and therapy of acne vulgaris.
- Describe risk factors for actinic keratosis.
- Design individualized treatment strategies for patients with actinic keratosis to reduce risk of squamous cell carcinoma.
- Summarize the efficacy and safety of fillers, toxins, devices, and techniques currently available in aesthetic and procedural dermatology.
- Identify the considerations in the selection of appropriate filler agents for treating different areas of the face.
- Compare and contrast the efficacy and safety of agents, devices, and techniques currently available in aesthetic and procedural dermatology.
- Determine the appropriate nonsurgical techniques for facial rejuvenation.
- Describe the appropriate use of neuromodulators in the treatment of the aging face.

- Use appropriate tools to accurately and promptly diagnose hair disorders.
- Select appropriate therapeutic strategies for alopecia areata based on patients' needs and desires.
- Apply treatment strategies for patients with atopic dermatitis based on disease severity with the goal of clear or almost clear skin.
- Incorporate strategies for use of use of new therapies aimed at blocking the inflammatory mediators of atopic dermatitis.
- Discuss the latest data on the prevalence, severity, and impact of primary axillary hyperhidrosis and other common forms of hyperhidrosis.
- Outline strategies for diagnosing primary axillary hyperhidrosis and other forms of hyperhidrosis, including the use of validated instruments to assess the impact of the condition on affected patients.
- Review the evidence regarding the efficacy and safety profile of various first-line and subsequent therapies for various types of hyperhidrosis, as well as patient candidacy for the different treatments.
- Increase evaluation and diagnosis of suspicious neoplasms.
- Identify treatment options for all stages of melanoma.
- Diagnose and treat onychomycosis in appropriately selected patients.
- Demonstrate in-depth understanding of onychomycosis treatments, including drug interactions and warnings regarding therapy in patients with comorbid disease or receiving other medications.
- Recognize different types of tinea infection.
- Describe the pathophysiology of psoriasis and the associated comorbidities of the disease.
- Diagnose and treat patients with psoriasis appropriately, based on current clinical guidelines.
- Compare and contrast safety and efficacy data on new and emerging therapies for psoriasis.
- Integrate biologic therapies into the management of appropriately selected patients with psoriasis.
- Monitor patient response to psoriasis therapy and modify the treatment strategy as needed.
- Develop self-education and patient education programs as part of the treatment plan for rosacea.
- Apply treatment strategies, based on knowledge of the indications, efficacy, and risks of available rosacea therapies, to achieve therapeutic goals in rosacea treatment.
- Develop a treatment plan to address hypertrophic scars and keloids.
- Differentiate seborrheic keratosis from other skin lesions, particularly melanoma.
- Match patients with the most appropriate interventions for effective and cosmetically acceptable treatment of SK lesions.

Evaluations From the 18th Annual Las Vegas Dermatology Seminar featuring the 14th Annual Psoriasis Forum

1. Participating in this educational activity changed my KNOWLEDGE. N=256

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
59%	34%	5%	<1%	1%

2. Participating in this educational activity changed my COMPETENCE. N=256

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
49%	37%	11%	<1%	2%

3. Participating in this educational activity changed my PERFORMANCE. N=256

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
47%	38%	13%	2%	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=212

Statement	% Responding
Implement a change in my practice/workplace.	29%
Seek additional information on this topic.	18%
Implement a change in my practice/workplace and seek additional information on this topic.	32%
Do nothing differently. Current practice/job responsibilities reflect activity recommendations.	19%
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 2017 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?"

- Early recognition of various skin conditions and treatment or referral.
- How I monitor MTX use; how I will select different biologic therapy in certain patients; how I will educate patients.
- Consideration of biologics.
- Application of enhanced knowledge and competency.
- I will change the considerations for systemic psoriasis treatment in relation to each patient's comorbidities. I will change the way I treat alopecia areata.
- I will educate my psoriasis patients on comorbidities and monitor that these comorbidities are being addressed by the appropriate providers (including myself).
- Incorporation of newer biologics and topicals for rosacea.
- I will look into using a newer biologic that offers higher PASI scores long term.

- Additional patient education, off label use of medications.
- More respect for psoriasis patients.
- Will change my prescribing habits based on the information provided.
- Feel more confident in treating acne, AKs
- Better confidence in the new IL-17 treatment for psoriasis, will be more apt to prescribe now.
- Include IL-17 inhibitors, TNF inhibitors and IL-23 inhibitors in my practice for psoriasis.
- Changes in monitoring of a few meds, less MTX med monitoring.
- I will approach the treatment of acne rosacea differently with the information I received. Additionally, while caring for patients with psoriasis I will be more likely to discuss other comorbidities associated with it.
- Will be more likely to use some of the newest biologics for psoriasis, use some of the newest treatments for eczema, and also perhaps decrease lab testing for isotretinoin monitoring.
- Will try zinc sulphate for warts and molluscum. Trial hyperthermia for molluscum. Will try adapalene for plantar warts. Will consider metformin use for HS
- Plan to use more IL-17 inhibitors in practice plan to incorporate new options in my rosacea patient treatment plan more likely to treat onychomycosis with oral terbinafine in recently infected patients.
- Since I came back already put a patient on vit B12 for aphthous ulcers partially in control with colchicine and another one on fexofenadine for alopecia areata. This 3 days seminar is a good complement for our daily clinic.
- More data on the biologics reinforce acne treatment in the direction of less antibiotics reinforce importance of vaccines great ideas with different treatment options.

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: Develop a comprehensive treatment plan for acne patients based on clinical guidelines, incorporating pharmacologic and nonpharmacologic strategies.

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]

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: Integrate into clinical practice the most recent research on the etiologies and therapy 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 J, 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.

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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: Describe risk factors 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. 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%. 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.

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: Design individualized treatment strategies for patients with actinic keratosis to reduce risk of squamous cell carcinoma.

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.

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. 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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Aesthetic and Procedural Dermatology

GAP: Clinicians are not adequately trained on the benefits and limitations of surgical and nonsurgical techniques as well as nonsurgical treatment options for aesthetic dermatology. The rapid rate of change within the field of procedural and esthetic dermatology, and increasingly, demands from patients, suggest the need for improved, increased, and more accessible training for clinicians.

Learning objectives:

- *Summarize the efficacy and safety of fillers, toxins, devices, and techniques currently available in aesthetic and procedural dermatology*
- *Identify the considerations in the selection of appropriate filler agents for treating different areas of the face.*
- *Compare and contrast the efficacy and safety of agents, devices, and techniques currently available in aesthetic and procedural dermatology.*
- *Determine the appropriate nonsurgical techniques for facial rejuvenation.*
- *Describe the appropriate use of neuromodulators in the treatment of the aging face.*

According to the American Society of Plastic Surgeons, more than 17.5 million cosmetic procedures were done in 2017, an increase of 2% from 2016.[ASPS 2017] The overall growth in cosmetic surgery continues to be driven by a significant rise in minimally invasive procedures: 15.7 million of the 17.5 million procedures were minimally invasive. In contrast to a 4% drop in facelifts and a 4% decrease in

neck lifts, there was a 2% increase in neurotoxin injections and a 3% increase in procedures involving soft tissue fillers. In fact, these two procedures have increased 819% and 312%, respectively, from 2010 to 2017.[ASPS 2017] The ASPS identified the top three procedures as:

- Botulinumtoxin (BoNT) type A injections: 7.2 million procedures
- Soft tissue fillers: 2.69 million procedures
- Chemical peel: 1.37 million procedures

Data from the American Society of Aesthetic Plastic Surgeons (ASAPS) identified the top 3 minimally invasive cosmetic procedures in women as BoNT injections, hyaluronic acid (HA) injections, and laser hair removal; in men, the most common procedures were BoTN injections, HA injections, and nonsurgical fat reduction procedures.[ASAPS 2018]

In the first of 3 recent articles by the Aesthetic Leaders in Facial Aesthetics Consensus Committee, the Committee noted that "as the number of physicians with limited experience in providing aesthetic treatment expands, the need for guidance and training from more experienced injectors has become apparent."[DeMaio 2017a] There has been rapid development of new devices and procedures, as well as new agents, often in the absence of comparative effectiveness research and patient-reported outcomes, making it challenging for clinicians to develop optimal cosmetic/aesthetic strategies.[Waldman 2017] In addition, dermatologists are now seeing more patients who are requesting these less invasive treatments, either as precursors to or instead of plastic surgery. Further, aesthetic dermatology is no longer limited to rejuvenating women's faces – there is a growing interest among male patients, and there are procedures that address the neck, décolletage, hands and arms. Dermatologists need to remain current with the various approaches and techniques for each of these concerns, Facial rejuvenation is clinically challenging but also can result in positive outcomes when clinicians are prepared and skilled at using procedures that result in age-appropriate aesthetic improvements.

Facial assessment: Traditionally the face is divided into three horizontal sections: upper face, midface, and lower face/chin. The neck has recently been added as a fourth potential section to be addressed. As rejuvenation approaches differ for each of these areas, it is imperative that cosmetic dermatologists consider the entire face before determining an appropriate rejuvenation strategy.[Sundaram 2015] In addition, dermatologists must be knowledgeable regarding the underlying facial anatomy, the structural and physiologic changes in the face associated with the aging process - including a loss of volume and a redistribution of fat -, and the visible consequences of photoaging.[Dhir 2016; Lambros 2007] Specifically, not all agents or techniques are appropriate – or safe – for all facial sections.

Volume loss is considered to be on the of the major contributors to facial aging, in turn, restoration of facial volume and contour changes has become an important treatment approach in the aesthetic field. The concept of gravity as the cause of facial aging has been gradually revised over the past 4 decades. During this time, pioneering research by investigators in the fields of plastic and reconstructive surgery and dermatology has consistently demonstrated facial aging involves changes on many levels, including bone structures, muscle strength, fat, and skin integrity. These changes, resulting from both intrinsic (age-related) and extrinsic ("environmental") factors, lead to modifications in the contours, shape, balance, and proportions of the face.

Generally, the upper face is considered a 'basic' area for neuromodulators, but an 'advanced' area for fillers.[De Maio 2017a] In contrast, fillers are considered 'basic' for the midface area, to provide volumizing and contouring.[De Maio 2017b] However, both the midface and lower facial areas require more knowledge and skill to address than the upper face, as there are increased risks of serious complications in these areas.[De Maio 2017b, 2017c]

Neurotoxins: Neurotoxin injections with botulinumtoxin type A are undeniably the most popular of all minimally-invasive cosmetic procedures.[ASPS 2017] Botulinumtoxin (BoNT) type A includes three distinct formulations: onabotulinumtoxin, abobotulinumtoxin, and incobotulinumtoxin. These 3 agents are not interchangeable -- each has distinct indications, and recommended doses and number of injections differ by agent and by injection location.[Carruthers 2018; Sundaram 2015] Further, there has recently been a move away from muscle paralysis towards neuromodulation through lower dosing and more frequent combinations with facial fillers.[Sundaram 2015] The effects are transient, lasting a few months.[Carruthers 2018] Cosmetic BoNT injections are predominantly used to address cosmetic concerns caused or exacerbated by muscle contractions – such as glabellar rhytides. Among the many other target areas are horizontal lines on the forehead, lateral canthal lines, and marionette lines.[Carruthers 2018] It is very important for clinicians to carefully screen potential candidates prior to treatment. Common complications include headache and transient bruising/swelling at the injection site(s); rare but potentially serious adverse effects include dysphagia, anaphylaxis, aspiration, pneumonia, and death.[Carruthers 2018]

Facial fillers: Whereas BoNT injections relax the underlying muscles that cause facial wrinkles, fillers are used to decrease the depth of lines or increase the size of specific facial structures. As such, BoNT is more often used in the upper third of the face, and fillers in the lower two-thirds. The last decade has seen the introduction of a multitude of new stimulatory and non-stimulatory soft tissue fillers for facial rejuvenation. Nonstimulatory fillers are more temporary, and do not stimulate collagenesis – whereas stimulatory fillers stimulate collagenesis and are thus considered to be permanent. Nonstimulatory fillers are generally comprised of hyaluronic acid (HA) or non-animal stabilized HA (NASHA). The non-HA fillers are comprised of calcium hydroxylapatite, poly-L-lactic acid (PLLA), poly-methyl methacralate microspheres (PMMA), or polyalkylimide (considered a semi-permanent filler that can be removed). Some of these formulations also contain lidocaine to limit injection site pain.

The increased availability of dermal filler options carries with it the inherent challenge of choosing the most appropriate agent (or combination of agents), including which agents are most appropriate to use to complement plastic surgery (when appropriate). As with the different formulations of BoNT, it can be challenging to remain current regarding the benefits, indications, facial locations, and techniques unique to the different fillers. Although not a new concept, the use of blunt cannulas to deliver fillers is on the rise due primarily to the fact that the filler can be injected with great precision with minimal bruising and bleeding as well as offers little downtime and discomfort.., .

Skin rejuvenation/resurfacing procedures: In addition to the improvement of age-related structural changes, facial rejuvenation also may require improvements in minor to major surface skin abnormalities or skin quality. Improvements of many superficial flaws may be accomplished nonsurgically with any of a number of topical medications (ie, retinoids and hydroquinone) and/or

resurfacing procedures (such as acid peels, dermabrasion, or laser resurfacing). Other patients require correction of more severe defects —particularly scarring from surgical or accidental wounds or burns, or those that occur as sequelae of skin disorders (especially severe acne). Although the desire for improved appearance motivates many patients to consult a practitioner for facial scar revision, others seek such treatment because of diminished function of the eyes, mouth, or nose. Effective and safe surgical and nonsurgical techniques are available, and chosen according to the cause, type, location, and pigmentation of the scar(s).

Body shaping/contouring: As newer treatments become available, dermatologists are also seeing the expansion of aesthetic medicine beyond the face to other parts of the body. Clinicians are now seeing more patients who seek body contouring and body rejuvenation through nonsurgical fat reduction. Cryolipolysis and ultrasonic energy both are non-surgical body shaping/contouring procedures that are on the rise. Cryolipolysis destroys subcutaneous fat cells by freezing them; therefore, cause cell death of subcutaneous fat tissue without apparent damage to the overlying skin. Other lipoplastic techniques currently are in development. One of these, known as focused ultrasound body contouring, uses low-intensity ultrasonic waves delivered across the surface of the skin. The device is said to work by destroying the membranes of subcutaneous fat cells.

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Alopecia Areata

GAP: Dermatologists lack knowledge regarding the diagnosis of hair diseases and thus may underestimate the effect of hair diseases on quality of life.

Learning objectives:

- *Use appropriate tools to accurately and promptly diagnose hair disorders.*
- *Select appropriate therapeutic strategies for alopecia areata based on patients' needs and desires.*

Alopecia areata (AA) is a common yet complex autoimmune disorder that causes nonscarring hair loss.[Darwin 2018] It is the second most common cause of hair loss and presents a challenge to treating physicians searching for effective treatment options, particularly since the disease can resolve spontaneously with no intervention. AA is believed to have a prevalence of between 0.1% to 0.2%, equating to affecting between 318,000 to 636,000 people in the US.[DHHS] It can manifest at any age, although the median age at diagnosis is 33.

A recent analysis of clinical practice gaps for dermatologists noted that, in general, dermatologists lack interest in caring for patients with hair complaints, such as alopecia, and underestimate the effect of hair complaints to patients' quality of life (QoL).[Colavincenzo 2016] In addition, lack of clinician knowledge and skill with diagnostic assessment of hair disorders leads to delays in diagnosis as well as misdiagnoses, which then impedes accurate treatment.[Colavincenzo 2016] It is crucial for the clinician to differentiate alopecia from other types of hair loss as it differs in prognosis and treatment. Although the diagnosis of AA can be made clinically, making an exact diagnosis is challenging.

AA generally develops suddenly, and typically manifests as smooth, clearly demarcated round patches of hair loss the size of a quarter. There can be "exclamation point" hairs around the periphery of the patches. In up to two-thirds of cases, patients with AA also have nail abnormalities, particularly nail pitting. While between one-third to one-half of patients recover within 1 year, up to 25% of patients will progress to alopecia totalis (AT; total scalp hair loss) or alopecia universalis (AU; total body hair loss).

AA is generally a clinical diagnosis which can be aided by a positive hair-pull test or trichoscopy; in rare cases, biopsy may be necessary. Histopathology varies according to disease stage. The exact

pathophysiology is unknown, but it is believed to be an autoimmune reaction to the hair follicles due to both genetic and environmental factors. Environmental factors are believed to exacerbate or induce AA; however, there is minimal scientific evidence supporting stress as a cause.[Gulec 2004; Gupta 1997; Braiac 2003] In 20% of cases, the patient with AA also has a family member with AA.[McDonagh 2002; Biran 2015]

There is no cure for AA. In some patients, it may spontaneously remit; when patients do have hair regrowth, it may take from months to years.[Pratt 2017] There are no known treatments that can completely restore hair, and patients with the disease experience significant psychological stress and emotional suffering. The most common treatment involves topical corticosteroids, which has been associated with a full response rate of approximately 57%.[Charuwichitratana 2000] Intralesional or systemic corticosteroids afford somewhat better results, but each has a greater adverse effect profile.[Kubevinie 1994; Jahn-Bassler 2017; Yoshimasu 2016; Kurasawa 2006] Other medications used to regrow hair include minoxidil, anthralin, the contact sensitizer Squaric acid dibutylester (SADBE), and diphenylcyclopropenone (also known as diphencyprone, DPCP). Clinicians should be aware that, regardless of therapy, there is a high rate of relapse.

Dermatologists have been studying genetic treatments in hopes of offering relief to patients. Key genes found in the GWAS include those linked to T-cell proliferation, and hair follicle genes that activate the NKG2D ligand, which can trigger autoimmunity. The findings suggest 3 avenues of treatment: blocking NK cell innate immunity, halting activated T-cells, and modifying the inflammatory cytokine network.

Investigational agents include low-dose interleukin (IL)-2,[Castela 2014] although there can be a paradoxical effect leading to exacerbations of AA.[Hordinsky 2014] A wide range of additional agents have been or are currently being investigated but have not demonstrated clear benefit. Among the other agents are phenol (carbolic acid); the anti-inflammatory bioflavinoid quercetin; the antidepressants tianeptine, imipramine, and paroxetine; and Janus kinase (JAK) inhibitors.[Xing 2014] In 2014, researchers identified the immune cells responsible for destroying hair follicles in people with AA and have tested an FDA-approved drug that eliminated these immune cells and restored hair growth in a small number of patients. Two FDA-approved JAK inhibitors tested separately—ruxolitinib and tofacitinib—were able to block these immune pathways and stop the attack on the hair follicles. The oral JAK inhibitors were shown to be effective for A, AT, and AU, but are associated with risks of serious adverse effects.[FDA-approved drug] Case studies suggest that topical ruxolitinib may be an effective approach that minimizes side effects otherwise associated with systemic administration.[Craiglow 2016] However, patients need to remain adherent to treatment or risk losing the regrown hair. Studies are also ongoing with tofacitinib.

Dermatologists are often challenged when treating patients with AA. The psychosocial consequences can be significant, and patients want treatments that are safe and effective and that prevent recurrences. At this time, however, there are no available treatments that can be recommended based on evidence of efficacy. Clinicians need to keep current regarding ongoing studies regarding investigational agents and approaches.

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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 patients with atopic dermatitis based on disease severity with the goal of clear or almost clear skin.

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]

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: Incorporate strategies for use of use of new therapies aimed at blocking the inflammatory mediators of atopic dermatitis.

The rationale for the development of new and emerging therapies for AD is the blockade of specific inflammatory mediators. The 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]

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
	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	OX40	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
	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-17 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
	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	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.

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 $\geq$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]

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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Hyperhidrosis

Hyperhidrosis – excessive sweating – significantly diminishes quality of life for the millions of people affected by the condition. [Doolittle 2016; Kamudoni 2017; Augustin 2013; Stolman 2008; Bahar 2016] In about two-thirds of cases, patients experience axillary hyperhidrosis, or excessive sweating in the underarms. [Doolittle 2016] Palmar hyperhidrosis (sweaty palms) is another common form of the condition.

In a recent report, Doolittle and colleagues concluded that previously published estimates of the prevalence of hyperhidrosis are outdated and underestimate the true prevalence of the condition. [Doolittle 2016] According to their survey of a nationally representative sample of 8160 individuals, those researchers estimate that the actual prevalence of primary hyperhidrosis (that is, excessive sweating that is not a secondary result from another medical condition) in the US population is 4.8% (15.3 million people), almost double the 2.8% rate for hyperhidrosis reported in a major study published 12 years earlier. [Doolittle 2016] Although numerous medical conditions and medications can cause excessive sweating, secondary hyperhidrosis is relatively uncommon, affecting only about 7% of patients. [Moraites 2014] Thus most patients will present with primary axillary hyperhidrosis.

Despite its prevalence, hyperhidrosis is underreported, underdiagnosed, and undertreated. [Moraites 2014; Glaser 2018; Pieretti LJ 2014] Effective treatments are available or are in late stages of clinical development. [American Academy of Dermatology; Grabell 2017; Hosp 2017; Sammons 2017; Glaser 2017] However, several gaps in clinician's knowledge and practice will need to be addressed so that patients with hyperhidrosis can benefit from those therapies. [Kerdel 2018; Glaser 2007]

Gap: Physicians do not appreciate the prevalence of primary axillary hyperhidrosis and other forms of hyperhidrosis and may be unaware of the impact these conditions can have on a patient's quality of life.

Learning objective: Discuss the latest data on the prevalence, severity, and impact of primary axillary hyperhidrosis and other common forms of hyperhidrosis.

The key gap to emerge from an extensive assessment of the evidence is clinicians' frequent failure to appreciate both the extent of hyperhidrosis and the impact it can have on an individual patient. [Doolittle 2016; Glaser 2007; Kerdel 2018; Pieretti 2014]

Patients and physicians alike contribute to the underrecognition of hyperhidrosis. According to Doolittle et al, only 51% of patients with hyperhidrosis have discussed their excessive sweating with a health care professional, mainly because they believe that hyperhidrosis is not a true medical condition and that no treatment options exist. [Doolittle 2016] Those attitudes may explain why, in a separate study involving 1,985 self-identified individuals with hyperhidrosis-, 85% waited at least 3 years before seeking medical help for their condition, and 48.9% waited 10 years or more. [Glaser 2018]

However, physician attitudes constitute another major barrier to effective management of hyperhidrosis. In one report, patient who are members of a hyperhidrosis support group told researchers that their experience of receiving a diagnosis had been "humiliating" and "belittling." [Kamudoni 2017] As these investigators report, "This was especially because the sweating problem was not taken seriously by the clinicians. For example, some participants reported being told that they were wasting their [clinicians'] time."

A self-fulfilling dynamic – in effect, a negative feedback loop – contributes to underrecognition hyperhidrosis, says Francisco Kerdel, MD, a dermatologist practicing in Coral Gables, Florida. "We don't appreciate the prevalence of hyperhidrosis, and thus we don't look for it or ask about in when evaluating patients," he explains. "Not spotting signs of hyperhidrosis or hearing patients report it contributes to our sense that it is uncommon." [Kerdel 2018] He notes that this complacent approach to hyperhidrosis may have its origins in medical school; dermatology residency programs devote scant attention to hyperhidrosis, and primary care training devotes little – if any – time to the condition. [Kerdel 2018]

In addition to underestimating the prevalence of hyperhidrosis, clinicians often fail to appreciate its impact on patients. [Doolittle 2016] "Current findings suggest that the severity and prevalence [of hyperhidrosis] are both higher than previously thought, indicating a need for greater awareness of the condition and its associated treatment options among medical professionals," note Doolittle and colleagues. [Doolittle 2016]

Those researchers found that 52% of patients reporting axillary hyperhidrosis said that their underarm sweating was barely tolerable or intolerable, and that it frequently or always interferes with daily activities. [Doolittle 2016] Patients also report significantly severe palmar hyperhidrosis. [Doolittle 2016] Because the mean age of onset of axillary hyperhidrosis among study subjects was 19 years, the effects of the condition can affect patients throughout their adult life. [Doolittle 2016]

In another study, interviews and online surveys with 71 people with hyperhidrosis found that:

- Nearly three-quarters reported an impact on lifestyle;
- 41% reported an adverse effect on leisure activities;
- One-third reported hyperhidrosis-related problems with performing daily household chores;
- 64% had concerns regarding other people's negative reactions to them; and,
- 69% said they had experienced embarrassment, anxiety, sadness, anger, or hopelessness as a result of their hyperhidrosis. [Kamudoni 2017]

That last finding, reflecting the psychological sequelae of hyperhidrosis, confirms other research showing that people with hyperhidrosis are roughly 3 times as likely as dermatology patients without hyperhidrosis to have anxiety and depression. [Bahar 2016] A study of more than 2000 consecutive patients presenting to dermatology clinics found that 21.3% of those with hyperhidrosis had anxiety and 27.2% had depression, compared with 7.5% and 9.7%, respectively, of patients without hyperhidrosis. [Bahar 2016] Multivariate analysis showed a positive correlation between the severity of hyperhidrosis and the prevalence of anxiety and depression prevalence. [Bahar 2016] Other research has shown elevated social stress levels and depressive symptoms in patients with primary hyperhidrosis relative to age- and sex-matched controls from the general population, with a subgroup of patients with axillary hyperhidrosis being most adversely affected. [Gross 2014] While the concomitant presence of hyperhidrosis and anxiety raises a "chicken-or-the-egg" question, several experts consider anxiety and depression to be sequelae of hyperhidrosis, while acknowledging that there also can be a vicious cycle of sweating prompting stress or anxiety, which prompts further sweating. [Gross 2014, Bahar 2016]

As Dr Kerdel states, "Dermatologists, primary care physicians, and also pediatricians have many educational needs related to hyperhidrosis, but the first and most important thing is recognizing how prevalent it is, and how deeply it can affect our patients." That awareness, he adds, is the key to setting an appropriate index of suspicion and to broaching the subject with patients in a manner that encourages candor. [Kerdel 2018]

Gap: Physicians face challenges in diagnosing hyperhidrosis, correctly identifying the various forms of the condition, and assessing the extent to which HH affects patients' daily activities and quality of life.

Learning objective: Outline strategies for diagnosing primary axillary hyperhidrosis and other forms of hyperhidrosis, including the use of validated instruments to assess the impact of the condition on affected patients.

Beyond recognizing sweating that exceeds the norm and then empowering patients to discuss their symptoms, perhaps the most difficult aspect of diagnosing hyperhidrosis may be the differential diagnosis. Dozens of medical conditions can cause secondary hyperhidrosis, ranging from the commonplace, such as acute febrile illness, diabetes, and menopause, to the rarely seen, such as pheochromocytoma, rickets, and Klippel-Trenaunay syndrome. [Moraites 2014]

Similarly, many medications can cause secondary hyperhidrosis as an adverse effect, including those that are used to treat pain, hypertension, endocrine disorders, erectile dysfunction, asthma, psychiatric conditions and other diagnoses. [Moraites 2014] Despite that laundry list of possible causes, however, a retrospective chart review examining the records of 415 hyperhidrosis patients seen at university-based dermatology department found that more than 93% had primary hyperhidrosis. [Walling 2011]

In practical terms, the diagnosis of hyperhidrosis is not necessarily complicated. Statistical analysis has shown that when a patient had excessive sweating of at least 6 months' duration, the presence of 4 or

more of the following characteristics allows the diagnosis of primary hyperhidrosis to be made with 99% sensitivity and 82% specificity:

- Primary involvement of eccrine-dense (axillae/palms/soles/craniofacial) sites
- Bilateral and symmetric sweating
- Absence of nocturnal sweating
- Episodes at least weekly
- Onset at 25 years of age or younger
- Positive family history
- Impairment of daily activities [Walling 2011]

Some experts believe the diagnosis can be streamlined even further. One recent approach holds that only at least 2, rather than at least 4, of these characteristics must to be present to fulfill the criteria for primary hyperhidrosis when secondary causes have been excluded. [Moraites 2014]

Applying these criteria, along with a physical examination and thorough medical and medication history, can reliably establish a diagnosis of primary or secondary hyperhidrosis. [Walling 2011; Moraites 2014] According to Dr Kerdel, however, physicians who ignore the obvious signs of hyperhidrosis also fail to identify the most likely explanation for the problem and thus may pursue extensive and expensive testing in search of an underlying condition. “In the great majority of cases, the hyperhidrosis is idiopathic, or primary, and not attributable to some other disease.” [Kerdel 2018]

Beyond classifying hyperhidrosis as primary or secondary in nature, the condition can be further characterized as generalized, regional, or focal. The extent and location of excessive sweating has important implications for treatment. [Moraites 2014]

Determining the severity of hyperhidrosis and the degree to which it interferes with daily activities and affects quality of life is another important component of the diagnostic process. Established instruments, such as the Hyperhidrosis Disease Severity Scale (HDSS), and newer resources, such as the Axillary Sweating Daily Diary (ASDD), have been validated and can provide clinicians with an efficient, consistent means of assessing the impact of hyperhidrosis. [Kowalski 2004; Glaser (ASDD) 2017] Educational activities that promote physician use of these validated tools are important because, in the words of one hyperhidrosis researcher, “Despite morbidity equal to other well-known dermatologic conditions, hyperhidrosis has historically been underacknowledged and undertreated because of the lack of accessible, scientifically accurate information and dispersal of that information within patient and medical communities.” [Pieretti 2014]

Gap: Physicians are not familiar with the range of approved and late-stage investigational first-line and secondary therapies for hyperhidrosis, or the candidacy criteria for each.

Learning objective: Review the evidence regarding the efficacy and safety profile of various first-line and subsequent therapies for various types of hyperhidrosis, as well as patient candidacy for the different treatments.

Hyperhidrosis is undertreated even though effective therapy is available. Topical, injectable, and oral medications, surgical management, and other interventions involving electrical or microwave techniques all can be employed in treating hyperhidrosis. [Stolman 2008; Grabell 2017] Given the high proportion of patients who have not yet sought medical attention for hyperhidrosis, and the importance of identifying and initiating treatment in those patients, [Moraites 2014] expanded options for first-line therapy may be particularly welcome and of interest not only to dermatologists but also to primary care clinicians. As Doolittle and colleagues note, "For individuals who seek treatment, their physicians will need more effective (first-line) treatment options at their disposal to have more confidence in identifying and diagnosing the condition." [Doolittle 2016]

Several topical anticholinergic agents are being developed to meet that need for additional first-line therapies. Current research is focusing on glycopyrronium tosylate (formerly DRM04), oxybutynin, sofpironium bromide, and umeclidinium, among others. [Grabell 2017]

Glycopyrronium tosylate is under review by the Food and Drug Administration (FDA) for the treatment of primary axillary hyperhidrosis. [Dermira 2017] The safety and efficacy of the medication relative to vehicle was assessed in the phase 3 ATMOS-1 and ATMOS-2 pivotal trials, which involved more than 690 patients. [Pariser 2017; Dermira 2016] The co-primary endpoints in both trials were the proportion of patients who achieved ≥4-point improvement from baseline in sweating severity as measured by the ASDD and the average absolute change from baseline in gravimetrically-measured sweat production. Secondary endpoints were the proportion of patients who had ≥2 grade improvement from baseline as measured by HDSS and the proportion of patients with at least a 50% reduction from baseline in gravimetrically-measured sweat production. All endpoints were assessed at the end of the 4-week treatment period. In ATMOS-2, glycopyrronium tosylate demonstrated statistically significant improvements in all primary and secondary endpoints relative to vehicle. [Pariser 2017; Dermira 2016] In ATMOS-1, the agent met the co-primary endpoint of reduction in sweating severity and both secondary endpoints. It also showed statistically significant improvement in reduction in gravimetrically-measured sweat production following exclusion of one outlier data center in accord with a pre-specified statistical analysis plan submitted to the FDA. [Dermira 2016]

Meanwhile, therapies involving the use of medical devices under study for their utility in treating hyperhidrosis include radiofrequency thermotherapy, laser therapy, and ultrasound therapy, among others. [Grabell 2017]

The expansion of the treatment armamentarium, while welcome, provides an information challenge to clinicians comparable to the need to fully appreciate the physical and psychosocial burden hyperhidrosis imposes on patients. As one team of researchers notes, "Physicians should understand the impact of focal hyperhidrosis and the need to stay abreast of the available treatment options to provide the best care for patients." [Glaser 2007] However, the critical prerequisite to enabling patients with hyperhidrosis to realize the benefits of those treatment options remains better identifying patients. "With a modest improvement in the recognition of hyperhidrosis, a provider has the opportunity to make a major impact on a patient's life." [Moraites 2014]

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Melanoma and Moles

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: Increase evaluation and diagnosis of 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 U.S. 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). 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] A noninvasive method to help distinguish between benign and malignant melanocytic nevi is through the use of clinical multiphoton microscopy images, which are able to quantitatively and qualitatively distinguish between the two.[Balu 2014]

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: Identify treatment options for all stages of melanoma.

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 approved only 2 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. 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, everolimus, and pazopanib.

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.

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GAP: Although more clinicians now appreciate that onychomycosis is a medically important condition, some clinicians and patients still regard it as a cosmetic problem with little clinical impact. Thus, onychomycosis may be untreated or undertreated.

Learning objective: Identify and treat onychomycosis in appropriately selected patients.

Onychomycosis is becoming recognized increasingly 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 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. In other specialties and in primary care, identification of nail fungus on the feet may not occur in the absence of a specific complaint by the patient, particularly because routine office visits usually do not involve removal of footwear (unless a patient has diabetes). 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.

When examination reveals signs of onychomycosis, the commonly used microscopic examination of a specimen prepared with potassium hydroxide (KOH) often suffices as a rapid, in-office diagnostic method. Tests including fungal culture and histopathology with periodic acid–Schiff (PAS) stain also are widely available and are frequently used. In special cases, immunohistochemistry, dual-flow cytometry, vivoconfocal microscopy, and scanning electron microscopy may be considered. In addition, polymerase chain reaction (PCR) testing techniques have received increased research attention in recent years and eventually may be more commonly used. However, for any of these tests to provide the most sensitive results, clinicians must obtain culture samples correctly and from the area between the normal and the diseased nail. 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]

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

Learning objective: Demonstrate in-depth understanding of onychomycosis treatments, including drug interactions and warnings regarding therapy in patients with comorbid disease or receiving other medications.

Treatment options currently approved in the United States for onychomycosis include oral and topical agents as well as laser therapy. Traditional oral agents include itraconazole and terbinafine; these drugs must be selected based on 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 others with underlying medical conditions such as diabetes.

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] Efinaconazole, a topical ointment approved in 2013, is first in the triazole class of agents to be developed for the treatment of distal lateral subungual onychomycosis. 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] In July 2014, the FDA approved tavaborole topical solution, 5%, the first oxaborole antifungal approved for the topical treatment of onychomycosis of the toenails resulting from infection with *Trichophyton rubrum* or *Trichophyton mentagrophyte*. Other classes of topical antifungals are being evaluated both in the United States and abroad.

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 triazole agent posaconazole also offer (off-label)alternatives 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, FDA-approved for tinea cruris and tinea corporis, has shown promising results in clinical trials for onychomosis.[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.

In some cases, other options may be considered, including surgery with Nd:YAG or diode lasers; photodynamic therapy; and mechanical, chemical, or surgical nail avulsion. Some patients may benefit from a combination of oral, topical, and surgical treatments.[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 unguium)
Terbinafine	Allylamine antifungal	Onychomycosis due to dermatophytes (tinea unguium)
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: Zane LT, et al, 2016.

Oral agents must be chosen for their activity against the involved pathogens (dermatophytes, nondermatophytes, 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]

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: Clinicians should be aware of the differential diagnosis of tinea and should recognize which treatments are – and are not – effective.

Learning objective: Recognize different types of tinea infection.

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. While tinea is a common and not serious, it can cause discomfort and is highly contagious.

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 ketoconazole poses a risk for severe liver injury, adrenal insufficiency, and drug interactions, and nystatin, while effective for *Candida* infections, is not effective against dermatophytes.

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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: Describe the pathophysiology of psoriasis and the associated comorbidities of the disease.

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: Diagnose and treat patients with psoriasis appropriately, based on current clinical guidelines.

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, cyclosporine, apremilast, 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 objectives:

- *Compare and contrast safety and efficacy data on new and emerging therapies for psoriasis.*
- *Integrate biologic therapies into the management of appropriately selected patients with psoriasis.*
- *Monitor patient response to psoriasis therapy and modify the treatment strategy as needed.*

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. Because psoriasis often requires long-duration treatment, it is imperative that agents demonstrate safety and persistence of benefit over extended periods. Recently, results from a 3 year study on ixekizumab, which selectively targets IL-17A, demonstrated its ability to sustain high responses with clearance of skin and nail lesions, with no new safety concerns.[Leonardi 2018] 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] In the recent global VOYAGE 1 and 2 trials, patients with moderate to severe plaque psoriasis were randomized to receive guselkumab, placebo followed by guselkumab, or adalimumab over a 24 week period.[Foley 2018] Compared with adalimumab, guselkumab was associated with significant improvement in scalp psoriasis and psoriasis on the palms and/or soles, suggesting dermatologists may need to include body regions affected when making treatment decisions.[Foley 2018] A number of other IL-23 antagonists are in late-stage development. There is evolving evidence suggestion IL-35 may be another possible target.[Li 2018] A biosimilar was introduced to the US market within the last year, and alternative maintenance regimens have been studied.

In May 2018, the FDA approved expanding the indication for certolizumab pegol to include adults with moderate-to-severe plaque psoriasis who are already candidates for systemic therapy or phototherapy. Certolizumab pegol is the first Fc-free, PEGylated anti-tumor necrosis factor treatment option to receive approval for this indication, based on findings from 3 phase 3 trials involving more than 1000 patients. [FDA 2018]

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
Certolizumab pegol	TNF-α	2018
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 A, et al, 2016; Blauvelt A, et al, 2017; Lee EG, et al, 2018; Reich K, et al, 2017

Agents under investigation

Biologic	Status	Target/Mechanism
Bimekizumab	Phase 2b	Dual inhibitor of IL-17A, IL-17F
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; Lee 2018

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]

In summary, advances in the understanding of psoriasis have led to new targeted therapies. Ongoing clinical trials have shown encouraging results for treating physical and psychological symptoms of

psoriasis. The findings of these trials support the idea that therapies targeting IL-23, specifically its p19 subunit, are effective against psoriasis while sparing IL-12. Long-term data from open-label extension studies would help guide clinical recommendations regarding the safety profiles of these agents and determine their long-term utility.[Lee]

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Rosacea

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

Learning objective: Develop self-education and patient education programs as part of the treatment plan for 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% of rosacea patients have reported reduced self-confidence and self-esteem, and 41% reported avoiding public contact, and 88% 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: Apply treatment strategies, based on knowledge of the indications, efficacy, and risks of available rosacea therapies, to achieve therapeutic goals in rosacea treatment.

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 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 inflammatory papules and pustules of mild to moderate 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 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/Keloids

GAP: Because keloids are typically benign, clinicians may not be current with the various treatments to remove these cosmetic growths.

Learning objective: *Develop a treatment plan to address hypertrophic scars and keloids.*

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 2017]

Standard treatment of hypertrophic scars and keloids comprises occlusive dressings, compression therapy, intralesional corticosteroid injections, and combinations of these therapies.[Berman 2017] 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 2017]

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 2017]

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 2013] 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 2013]

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 2017]

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Seborrheic Keratosis

GAP: Because seborrheic keratoses are almost always benign and usually do not require medical intervention, clinicians tend to overlook the importance of these lesions to patients.

Learning objective: Differentiate seborrheic keratosis from other skin lesions, particularly melanoma.

Seborrheic keratosis (SK) is among the most common dermatologic diagnoses, found in some 83 million Americans—approximately 20%-25% of the population.[Jackson, DelRosso] These benign lesions are usually seen in people older than 50 years. SK lesions are equally distributed among men and women, although a recent survey of SK patients found a slightly higher rate among men.[DelRosso] SK is thought to be more prevalent in Caucasians, but a variant form, known as dermatosis papulosa nigra, can affect people with Fitzpatrick VI skin type.[Hafner 2008]

Patients often present to their clinicians because they are concerned about potential malignancy or the unsightliness of the condition.[DelRosso] Many dermatologists do not routinely recommend treatment for benign SK lesions unless the lesions have become irritated, leading to pruritus and bleeding.
The challenge for clinicians is that benign tumors may masquerade as more serious skin lesions, such as melanoma in situ or squamous cell carcinoma. SK are usually distinguished by the horned cysts that can be seen on dermatoscope examination.[Hafner 2008]

Differential Diagnoses of Seborrheic Keratosis

Premalignant or malignant lesions

- Actinic keratosis
- Bowen disease (squamous cell carcinoma [SCC] in situ)
- Invasive SCC/SCC in situ
- Lentigo maligna
- Malignant melanoma
- Pigmented basal cells

Benign lesions

- Acrochordon (skin tags)
- Acrokeratosis verruciformis
- Benign lichenoid keratosis
- Condyloma acuminata
- Eccrine poroma/hidrocathoma simplex
- Melanocytic nevus
- Solar lentigo (liver spots)

- Tumor of the infundibulum
- Verruca vulgaris (warts)

Source: Jackson JM, et al, 2015

Because SK is among the most frequently diagnosed lesions in dermatology, clinicians can become complacent about its diagnosis. Such complacency should be avoided; in a retrospective study of 577 SK lesions, 6.4% were eventually found to be malignant tumors.[Eads] A timely diagnosis that differentiates SK and melanoma is essential for long-term survival. Melanomas that are <1 mm in depth have a 95% 5-year survival rate, which drops to 45% for melanomas >4 mm thick.[Vestergaard] Another diagnostic tool, the 7-point checklist, assigns a score to assess the severity of lesions;[Walter] a high-scoring lesion should be referred to a dermatologist.[Walter]

Experienced dermatologists can easily distinguish SK from more serious and potentially malignant lesions. At minimum, visual examination under proper lighting will aid the diagnosis. Use of a dermatoscope, following proper training, reduces misdiagnoses and unnecessary biopsies.[Carrera; Vestergaard]

GAP: The use of the currently available treatments (ie, destructive modalities: cryosurgery, curettage, electrodesiccation, excision) often produces undesirable cosmetic outcomes, including scarring and hyper- and hypopigmentation.

Learning objective: Match patients with the most appropriate interventions for effective and cosmetically acceptable treatment of SK lesions.

Depending on the location of one or more SKs, the impact on patients' quality of life can be considerable. Without treatment, these pigmented, macular or papular lesions gradually increase over time in size, thickness, and/or color. Moreover, many patients have multiple SKs. Clinicians must accurately diagnose SK lesions before removing them. SK lesions are usually benign and can be removed for cosmetic reasons if the patient desires; treatment may be indicated—and reimbursable—if the lesion is irritated. In the case of suspicious lesions, clinicians should perform a shave biopsy to ensure that the mostly benign lesions are not premalignant or malignant, such as melanoma.

The currently available options for treatment (ie, removal) are modalities that rely on tissue destruction—cryosurgery, curettage, electrodesiccation, and excision). Thus, scarring and hyper- or hypopigmentation are potential sequelae of treatment. When SKs appear on a cosmetically sensitive area such as the face, the treating clinician confronts a challenge in patient selection and choice of treatment modality; the patient confronts the choice between living with the lesions or risking a cosmetically unacceptable outcome.

There are no guidelines or efficacy studies on the best way to remove SK lesions. Choice of treatment is based on the number of lesions, location on the body, skin pigment, depth of lesion, and patient esthetics. Cryosurgery is the preferred method for removing most lesions. Other methods include curettage, electrosurgery, lasers and combinations of modalities. The American Academy of

Dermatology recommends that any clinician using cryosurgery, curettage, or lasers be properly trained.[Jackson]

There are currently no FDA-approved topical treatments for SK; however, several such therapies are in development. The emergence of novel noninvasive and topical formulations is expected to provide more cosmetically elegant solutions for destroying SK lesions without scarring, dyspigmentation, or infection.[Jackson]

Preliminary evidence shows promise for an agent in development, a high-concentration hydrogen peroxide topical known as A-101 40% solution, which must be applied by a dermatologist as an in-office procedure.[Aclaris PR] In 2 pivotal phase 3 trials (N=937), 51.3% of patients treated with the solution achieved the primary end point: clearance of all 4 treated SK lesions on the face, trunk, or extremities, compared with a clearance rate of 7.3% in patients given placebo.[Aclaris PR, Clinicaltrials.gov] For facial lesions, A-101 40% solution cleared 65.3% of all 4 lesions vs 10.5% for placebo.[Aclaris PR, Clinicaltrials.gov] Treatment-related adverse reactions, such as hypopigmentation, hyperpigmentation, and scarring occurred in <1% of patients in a subsequent open-label study.[Aclaris PR] A new drug application for A-101 40% solution has been submitted to the FDA for review; a decision is expected by the end of 2017.

Other topical agents under study have reported only small case studies to date. These include: 5% potassium dobesilate cream, which inhibits the skin's FGFR3 activity to halt SK formation [Cuevas]; BL-05010, a combination of aqueous trichloroacetic acid (TCA) and formic acid, which is applied topically with a pen device, and is currently in phase 2 trials [Levy-Nissenbaum 2015]; and tazarotene 0.1% cream, which was more effective than calcipotriene ointment and imiquimod cream in a small, open-label study.[Herron 2004] The nonsteroidal anti-inflammatory drug, diclofenac gel 3%, showed promise in one case study.[Aktas] Though diclofenac gel is approved for clearing actinic keratosis, it may provide another (off-label) option for those whose SK lesions are in cosmetically sensitive areas. Topical and systemic vitamin D were marginally effective (30% clearing) in small open studies, but recurrence was common.[Brodsky 2009;Mitsuhashi] A meta-analysis reported that evidence suggests topical vitamin D is ineffective in the treatment of actinic keratosis, seborrheic keratosis, and several other conditions.[Wat]

Noninvasive treatment using intense pulsed light (IPL) to treat SK lesions has been tested in small case studies with positive results, albeit with small, superficial lesions.[Piccolo] Researchers caution that results can vary according to the clinician's experience with IPL.

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