PEDIATRIC DERMATOLOGY

JUNE 2018

Tips for spotting allergic contact dermatitis in children

When to worry about congenital melanocytic nevi

Atopic dermatitis gets new therapies

How to get through the tough talks about alopecia areata

Commentaries by Lawrence F. Eichenfield, MD & Robert Sidbury, MD, MPH

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1. *J Drugs Dermatol* (2015);14:478-485.
2. Data on file.

Keep an eye out for skin conditions

BY LAWRENCE F. EICHENFIELD, MD

IN THIS ISSUE, we highlight challenging birthmarks, including ulcerative hemangiomas and congenital melanocytic nevi with multiple satellite lesions. Hemangioma management has been transformed by the use of oral propranolol and topical timolol; these therapies work best when started early, so it is important to keep an eye out in the first few months of life for lesions amenable to treatment. Remember that facial or scalp hemangiomas that are 5 cm or larger may be associated with PHACE syndrome and require early specialist evaluation and imaging of the brain, great vessels, and heart.

Melanocytic nevi, both congenital and acquired, can be straightforward ... or not! Lesions, including Spitz nevi, can be benign or atypical and may require biopsy, excision, or serial follow-up. A set of articles discusses the great strides being made in atopic dermatitis and psoriasis, including insights into disease presentation, comorbidities, and an expanding set of topical and systemic therapies including biologic agents.

Allergic contact dermatitis should be kept in mind whenever a localized or atypical-appearing dermatitis presents, and the chemicals in personal care products should be considered as allergens. Other interesting topics covered include management of Stevens-Johnson syndrome and toxic epidermal necrolysis, and fake and fraudulent drugs that have appeared around the world as well as in the United States.

Dr. Eichenfield is chief of pediatric and adolescent dermatology at Rady Children's Hospital–San Diego. He is vice chair of dermatology and professor of dermatology and pediatrics at the University of California, San Diego. He received research support and/or consulting fees from Amgen, Anacor/Pfizer, Dermira, Leo, Lilly, Regeneron/Sanofi, Novan, Novartis, and Valeant.

Skin disorders that hurt the soul

BY ROBERT SIDBURY, MD, MPH

A COMMON THEME uniting several of the articles is the discordance between impact on medical and psychological well-being.

Primary focal hyperhidrosis is a condition that many children suffer for years before bringing it to medical attention, in part because they feel medically well. Psychologically, it can be a different story. A patient whom I first met when he was 12 years of age told the story through tears of other kids not wanting to hold his hand in "ring around the rosy" years earlier; such stories are unfortunately not uncommon. Likewise, patients with extensive alopecia areata typically are very healthy but can be devastated by the loss of their hair; providers must consider the complex psychology of this disorder for patient, family members, and even themselves.

Hidradenitis suppurativa patients generally present around the onset of puberty with draining lesions classically in the axilla and groin, areas generally hidden from view. The embarrassment many affected kids feel may prevent them from bringing it to medical or even parental attention. Although associated comorbidities such as obesity may be present, the greatest short-term "harm" can be psychological. Pediatricians must therefore make a point to find these diagnoses when they don't present spontaneously and manage beyond the walls of the pharmacy. We also will discuss a number of other common (tinea capitis) and rare (epidermolysis bullosa) conditions, closing out with a review of infestations just in time for summer!

Dr. Sidbury is chief of dermatology at Seattle Children's Hospital and professor of pediatrics at the University of Washington, Seattle. Relative to the commentaries, Dr. Sidbury has no financial disclosures or conflicts of interest.

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MDedge FRONTLINE MEDICAL COMMUNICATIONS

Expert shares tips for spotting allergic contact dermatitis in children

BY DOUG BRUNK
REPORTING FROM WCPD 2017

CHICAGO – If severe eczema persists in a pediatric patient despite your best treatment efforts, think allergic contact dermatitis.

"Or, if your eczema patients tell you that they have a cream that's making things worse, you should think about a contact allergen," Catalina Matiz, MD, said at the World Congress of Pediatric Dermatology.


DR. MATIZ

Allergic contact dermatitis (ACD) is a type IV delayed-type hypersensitivity reaction to haptens that come into contact with the skin. Poison ivy is a common plant-based culprit, while nickel is the most common metal allergen in adults and children. "The skin barrier also plays a role," said Dr. Matiz of the department of dermatology at Rady Children's Hospital–San Diego, and the University of California, San Diego. "Compared with adults, children have a thinner stratum corneum, and some haptens can penetrate the skin. Some studies suggest that patients with atopic dermatitis may have increased rates of allergic sensitization, and filaggrin mutations have been found in patients with atopic dermatitis and in patients with ACD to nickel. Filaggrin helps to aggregate the cytoskeletal proteins that form the cornified cell envelope. Without filaggrin, the skin barrier is defective."

Atypical locations for atopic dermatitis (AD) that should make you think of allergic contact dermatitis include the eyelids, perioral area, scalp, neck, extensor surfaces, hands and feet, and genitalia. First-line treatment involves an adequate potency of corticosteroids. "Most of the time, you need mid- to high-strength corticosteroids for body lesions," Dr. Matiz said. "If you suspect poison ivy or severe contact reactions, you may need to treat with systemic corticosteroids with a slow taper of 3-4 weeks. It's important to improve the skin barriers with the use of moisturizers, and you want to limit the use of irritant products as well. These include fragrances, formaldehyde, and cocamidopropyl betaine. Avoidance of the suspected culprit is very important."

The top 10 pediatric allergens found in personal hygiene products across five studies in the medical literature include neomycin, balsam of Peru, fragrance mix, benzalkonc ium chloride, lanolin, cocamidopropyl betaine, formaldehyde, methylchloroisothiazolinone/methylisothiazolinone, propylene glycol, and corticosteroids. Dr. Matiz makes it practice to patch test as a last resort. "I always try to get a history, try to improve their symptoms, and have them start avoidance first, following the preemptive avoidance list," she said (Expert Rev Clin Immunol. 2016;12[5]:551-61).

The T.R.U.E. test includes 35 allergens. "The T.R.U.E test is a good tool, which can capture up to 70% of relevant reactions in children with the inconvenience that some of the allergens in the test are not that relevant in children, and it's not yet [Food and Drug Administration] approved to use in children," she noted. The comprehensive chamber test allows you to select from unlimited number of allergens, "but that's difficult. You have to have specialized staff to help you make the cells."

A list of the minimum 20 allergens you should test for in children and the recommended supplemental allergens depending on history and locations of their dermatitis can be found in the following article: Curr Allergy Asthma Rep 2014;14[6]:444. "I always tell patients when they come for consultations to bring in everything they're using: their shampoos, creams, and medications, because we want to see what they're exposed to, so we can select the right allergens and also test their own products," Dr. Matiz said. She recommends avoiding testing for strong sensitizers such as paraphenylenediamine, in children younger than 12 years of age who don't have a history of exposure.

CHILDREN HAVE A THINNER STRATUM CORNEUM, AND SOME HAPTENS CAN PENETRATE THE SKIN.

Testing tips for children younger than age 5 yearw include decreasing concentrations to half for nickel, formaldehyde, and rubber accelerators. "Don't test for paraphenylenediamine unless there is high suspicion," she said. "Consider removing patches by 24 hours in the very young."

The best antidote to contact dermatitis is avoidance of the known trigger. "You want to spend a lot of time with patients and parents on this," she advised. "Give a list of safe products to use from the American Contact Dermatitis Society's Contact Allergen Management Program [www.contactderm.org], and provide handouts about the location and history of positive allergens [www.truetest.com]." And, she added, "make a plan of treatment and follow up in 6 weeks."

Dr. Matiz disclosed that she is a subinvestigator in the Clinical Evaluation of T.R.U.E Test Panel 3.3 in Children and Adolescents study.

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COMMENTARY **BY DR. EICHENFIELD**

MAKING THE DIAGNOSIS of allergic contact dermatitis (ACD) can be difficult, and often is delayed. While some common, acute exposure-related ACD can be straightforward to diagnose, such as poison ivy and poison oak, other exposure-related ACD can be more difficult, especially as the "culprits" vary over time. ACD can be a factor for exacerbation of atopic dermatitis as well as an alternative diagnosis.

The expert experiences discussed in the articles stress several allergens that can be present in a variety of personal care products, including fragrances, methylchloroisothiazolinone/methylisothiazolinone, balsam of Peru, benzalkonium chloride, lanolin, cocamidopropyl betaine, formaldehyde, and propylene glycol.

Dr. Cory Dunnick stresses that shampoos and body washes may be a common source of ACD and that there can be irritant effects from surfactants and alkyl glucosides. The finding that liquid soaps might be more risky for sensitive patients than bar soaps is interesting, as the liquid soaps had more preservative and surfactant allergens.

And the story of methylisothiazolinone, which was thought to have a low risk for allergenicity, has become a common concern with its being utilized over the past decade in body washes and disposable wipes, winning it the "award" as the "Contact Allergen of the Year 2013" by the American Contact Dermatitis Society.

Dr. Alina Goldenberg stressed that 20% of 152 pediatric skin care products at major retail stores contained methyl -isothiazolinone, and that a registry of pediatric dermatology contact dermatitis found increasing positive patch tests to both methylchloroisothiazolinone and methylisothiazolinone.

A great takeaway is that atypical locations and distributions for dermatitis should make you think of ACD, and the accompanying articles discuss some of the particularities of approaches to patch testing in children. We also should remember that allergies to metals are quite common, especially to nickel, and that metal implants may be an occasional but important source of allergy.

Bar soaps may be better than body washes for contact dermatitis patients

BY JIM KLING
REPORTING FROM PDA 2017

SAN FRANCISCO – Chronic contact dermatitis often is tied to hidden allergens found in shampoos, soaps, and body washes, according to Cory Dunnick, MD. "A lot of patients who get referred to my patch test clinic will have chronic dermatitis that isn't responding to treatment or is worsening despite treatment, or they present with a pattern that is suggestive of contact dermatitis," she said in an interview.

There also is a common perception that liquid body washes are better than bar soaps because they may be more moisturizing, but the results of a recently published study suggest otherwise, said Dr. Dunnick of the department of dermatology at the University of Colorado at Denver, Aurora, at the annual meeting of the Pacific Dermatologic Association.

In a discussion of hidden allergens in shampoos and soaps, Dr. Dunnick observed that shampoos are a common source of contact dermatitis and that alkyl glucosides and mild surfactants, which generally have low irritancy, are frequent culprits as well. In 2013, 19 of these compounds were declared safe by the Cosmetic Ingredient Review Expert Panel (Int J Toxicol. 2013 Sep-Oct;32[5 Suppl]:22S-48S).

Dr. Dunnick was one of the investigators in a study that compared ingredients in the top-selling 50 bar soaps and 50 body washes on Amazon.com to determine if there was a difference with respect to allergen content. They

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PIROTEHNIK/ISTOCK/GETTY IMAGES

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obtained the ingredients list for all the products and compared them with the American Contact Dermatitis Society Core Allergen Series. Counter to the common belief, results of the study indicated that liquid soaps were likely the worse choice for sensitive patients: They contained far more preservative and surfactant allergens than did bar soaps, and there was no difference in fragrance content between the two classes (Dermatitis. 2017 May 23. doi: 10.1097/DER.0000000000000289).

Of the 50 liquid soaps, 44 had one or more preservative allergens, compared with none of the bar soaps (*P* less than .001), and 34 had at least one surfactant allergen, compared with seven of the bar soaps (*P* less than .001). Of the body washes tested, 48 had fragrance, as did 47 of the bar soaps.

The most common allergens in body washes were methylisothiazolinone (MI; 19 of 50), quaternium-15 (16), sodium benzoate (15), methylchloroisothiazolinone/methylisothiazolinone (12), DMDM hydantoin (10), and phenoxyethanol (9). None of these allergens appeared in any of the bar soaps.

"If you have a patient who you suspect has a contact allergy to a preservative or surfactant ingredient, then you can recommend perhaps switching to a bar soap, maybe one that is fragrance free," advised Dr. Dunnick.

The most common allergen they found in body washes, MI is becoming an increasing concern, she said. It has been around for many years but became more prevalent when the Food and Drug Administration decided in 2005 to allow higher concentrations of MI to be used in skin care products. "It's a pretty strong sensitizer. As a result, we're seeing a lot more allergy," she noted.

DR. DUNNICK

And MI dermatitis can be challenging to diagnose. The dual methylchloroisothiazolinone/MI test, which most dermatology offices have on hand, is not sufficiently sensitive and can miss almost 40% of MI allergies, according to Dr. Dunnick. Instead, she recommended a test specific to MI, which usually has to be specially ordered.

This soap/body-wash allergen study sends a clear message to dermatologists to individualize recommendations, she said. "A lot of dermatologists recommend what they think are mild soaps, but they don't necessarily think about what contact allergens might be in those soaps, so maybe they need to make more specific recommendations. They might recommend Dove soap," but there are different types of Dove soaps, she pointed out.

A bigger challenge is finding a shampoo for sensitive patients. Almost all contain fragrances, and MI is an ingredient in many shampoos as well. Dr. Dunnick has found the DHS brand, which is fragrance free, to be helpful in some cases, and the Nonscents brand, also fragrance free, is sometimes recommended as safe.

But, in the end, recommendations must be individualized to the patient's specific allergies, and that requires a thorough work-up. "You don't know what they are unless you do the patch test," she said.

Dr. Dunnick reported having no relevant financial disclosures.

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Metals may surprise you as the sources of contact dermatitis

BY HEIDI SPLETE

REPORTING FROM SDEF WOMEN'S & PEDIATRIC DERMATOLOGY SEMINAR

Clinicians faced with baffling contact dermatitis patients should expand their view of potential causes to include metals anywhere in the body, according to Jennifer H. Perryman, MD, of the Greeley Skin Clinic in Fort Collins, Colo.

For example, metal from orthopedic implants can cause contact dermatitis, Dr. Perryman said at Skin Disease Education Foundation's Women's & Pediatric Dermatology Seminar.

The cutaneous complications of metal implants generally are eczematous, but they can be urticarial and vasculitic as well, with symptoms either generalized or localized. Dr. Perryman explained. Noncutaneous complications from contact dermatitis associated with the metal include chronic joint pain, and a loosening and dysfunction of the device.

FOR EXAMPLE, METAL FROM ORTHOPEDIC IMPLANTS CAN CAUSE CONTACT DERMATITIS.

It is a case of "chicken or the egg: Metal allergy causes device failure, or device failure causes metal allergy," Dr. Perryman said.

Dental implants also can be unforeseen causes of contact dermatitis, she noted.

The bone cement used in some

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Isothiazolinone sensitivity causing contact dermatitis is frequent and underdiagnosed

BY MARY ANN MOON
FROM PEDIATRIC DERMATOLOGY

Sensitization to the isothiazolinones MCI (methylchloroisothiazolinone) and MI (methylisothiazolinone), which are used as preservatives in a wide variety of personal and household products, is both frequent and underdiagnosed in U.S. children, according to a report published in the journal Pediatric Dermatology.

These agents are compatible with surfactants and emulsifiers, and because they maintain biocidal activity across a broad range of pH levels they are frequently used as preservatives in products such as wet wipes; shampoos and hair conditioners; soaps, cleansers, and disinfectants; and laundry products. However, they are known to cause contact dermatitis very frequently, and are among the top five contact allergens identified in infants' patch tests.

A recent survey showed that among 152 pediatric skin care products available at major retail stores, 20% contained MI. These were specifically targeted to infants and children, advertised as being "hypoallergenic," "natural," good for "sensitive" skin, and containing "gentle ingredients," said Alina Goldenberg, MD, of the department of dermatology at the University of California, San Diego, and her associates.

During the past 10 years, only 35 U.S. cases of a positive patch-test reaction to MCI and/or MI have been reported in the literature. To get a more accurate estimate of the true prevalence of pediatric sensitization to MCI and MI, the investigators analyzed information in a database of patch-test results, the Provider Contact Dermatitis Registry. They focused on 1,056 patch tests performed during a 1-year period.

AMONG 152 PEDIATRIC SKIN CARE PRODUCTS AVAILABLE AT MAJOR RETAIL STORES, 20% CONTAINED METHYLISOTHIAZOLINONE.

They found 37 positive reactions to combined MCI/MI and another 39 reactions that were negative to combined MCI/MI but positive to MI alone. This shows how important it is to test for sensitization to both formulations separately, Dr. Goldenberg and her associates noted.

In stark contrast to the reported 35 cases across the entire country during a 10-year period, the investigators found 76 cases (1%) in 1,056 patch tests during a 1-year period.

When test results for MCI/MI and MI alone were compared with those for all other allergens, children sensitized to the isothiazolinones showed marked differences: They were significantly younger, and the location of their dermatitis was more likely to involve the groin and buttocks. This probably is due to the increased use of wet wipes containing MCI and MI being used to clean up urinary and fecal accidents in young children, the researchers said.

The Society for Pediatric Dermatology supported the work. Dr. Goldenberg reported having no relevant financial disclosures; an associate reported serving as a consultant for Johnson & Johnson.

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SOURCE: Goldenberg A et al. Pediatr Dermatol. 2017 Mar;34[2]:138-43.

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implants may contain a variety of potential irritants such as methyl methacrylate, *N,N*-dimethyl-p-toluidine (DPT), benzoyl peroxide, gentamicin, and hydroquinone.

Metal allergy in the mouth most often presents as a reaction resembling oral lichen planus, with lesions that are reticular, atrophic, erosive, or plaque-like. These lesions usually erupt next to the implant, she said. Some patients also experience burning mouth syndrome from amalgam tattoos. However, some patients who test positive for metal allergies in general have developed a tolerance for dental implants as a result of having worn braces in the past.

Metal eyelid weights implanted to treat lagophthalmos are another rare but potential allergen to consider, said Dr. Perryman.

These weights often are made of gold, and Dr. Perryman cited a study in which four patients with gold eyelid weights experienced inflammatory reactions. Patch testing revealed gold sodium thiosulfate as the cause of their allergic contact dermatitis (Dermatitis. 2008 May-Jun;19[3]:148-53).

Other options for these patients include platinum weights, hyaluronic acid, ointment, and taping, she commented.

Dr. Perryman had no financial conflicts to disclose. SDEF and this news organization are owned by the same parent company.

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When you should worry about two or more congenital melanocytic nevi

BY M. ALEXANDER OTTO
EXPERT ANALYSIS FROM SDEF HAWAII DERMATOLOGY SEMINAR

KAUAI, HAWAII – Children born with two or more melanocytic nevi of any size should have an MRI to check for brain lesions, ideally within the first 6 months, according to Jennifer Huang, MD, a pediatric dermatologist at Boston Children's Hospital.

Two or more nevi increase the risk of CNS involvement, which in turn increases the risk of malignant conversion by more than 16-fold.

Dr. Huang's advice came during a presentation at the Hawaii Dermatology Seminar provided by the Global Academy for Medical Education/Skin Disease Education Foundation.

Among the studies she cited was a 2017 literature review of 448 children with congenital nevi, 10 of whom developed melanoma: It arose in the skin in 2, the brain in 6, and an unknown location in 2. All 10 children were born with two or more nevi, and not all of them had large or giant nevi, which is a known risk factor for malignant conversion (Br J Dermatol. 2017 May;176[5]:1131-43).

"If the scanning brain MRI is normal, [children] might not have congenital melanocytic nevus syndrome, and would be at low risk for melanoma," Dr. Huang said. "If it's abnormal, they might be at high risk for melanoma." In the 2017 study, the odds ratio for melanoma with an abnormal MRI was 16.7 ($P = .001$).


DR. HUANG

Both melanocytes and neuronal cells arise from the embryonic neural crest, which explains the link between congenital nevi and brain lesions. Almost all congenital nevi are associated with early postzygotic mutations in the NRAS gene, and it's possible the mutations affect other neural crest cell lines, including in the CNS, she said.

It's also important to remember that childhood melanoma often doesn't follow the ABCDE (asymmetry, border irregularity, color not uniform, diameter greater than 6 mm, and evolution) signs of melanoma common in adults.

In a retrospective study of 70 children with melanoma or ambiguous melanocytic tumors, 40% of pubertal subjects and 60% of prepubertal participants did not meet conventional adult ABCDE criteria. The majority of cases were raised, even in color, less than 6 mm across, symmetric, and de novo (J Am Acad Dermatol. 2013 Jun;68[6]:913-25).

It turns out that rapid evolution in size, shape, and color is the No. 1 unifying factor in childhood melanomas. Other key clues include raised lesions with uniform color or no pigmentation at all. A modified ABCDE for pediatric melanoma has been proposed: amelanotic, bump/bleeding, color uniformity, diameter variability, de novo, and evolution.

"The lesson to learn is not to ignore the traditional ABCDEs of melanoma, but to recognize that pediatric melanoma may present with different clinical characteristics, and to incorporate this awareness into our practice," Dr. Huang said.

She did not have any disclosures. SDEF/Global Academy for Medical Education and this news organization are owned by the same parent company.

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COMMENTARY **BY DR. SIDBURY**

CONGENITAL MELANOCYTIC NEVI can pose two separate but related risks: melanoma and neurocutaneous melanosis. Dr. Jen Huang recommends MRI screening for any infant born with two or more congenital melanocytic nevi regardless of size. A positive MRI confirms a diagnosis of neurocutaneous melanosis and a higher risk for CNS melanoma and neurologic compromise. In the setting of a negative MRI, melanoma risk is likely size related with small-to medium-sized nevi (less than 20-cm final size) having no greater risk than any nevus that children may acquire during their lifetime.

Dr. Huang also reminds us that in any circumstance, pediatric melanoma can present atypically. She cited a 2013 review at the University of California, San Francisco, that noted fewer than half of all pediatric melanomas at their institution over a 25-year period "obeyed" the traditional ABCDE (asymmetry, border, color, diameter, and evolution) melanoma detection criteria.

Pediatric melanoma more commonly arises de novo, changes rapidly, and can completely lack signature pigment (a.k.a. amelanotic melanoma). These factors are all made more difficult in large congenital melanocytic nevi given their inherently heterogeneous size, shape, color, and texture. Annual skin exams and vigilance at home for any change in appearance, texture, or symptoms are essential to best outcomes.

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Hidradenitis suppurativa diagnosis typically is delayed in children

BY HEIDI SPLETE

Children with hidradenitis suppurativa (HS) may suffer with symptoms for an average of 7 years before they are diagnosed, according to pediatric dermatologist Anna Yasmine Kirkorian, MD.

Data from a 2015 study showed that 73% of pediatric patients with HS were diagnosed more than 2 years after the onset of symptoms, said Dr. Kirkorian of the department of dermatology at Children's National Health System and George Washington University, Washington. (Br J Dermatol. 2015 Dec;173[6]:1546-9).

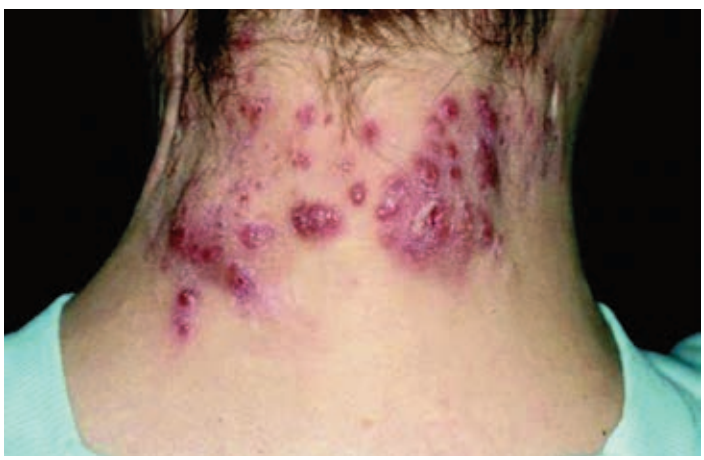
DR. KIRKORIAN

The characterization of pediatric HS in the literature needs to be improved so that adult style therapeutics can begin to be applied in pediatric clinical trials, she said at a hidradenitis suppurativa symposium at George Washington University in Washington.

Genetics can play a role in HS, likely via mutations in the gamma-secretase protein that leads to epidermal differentiation and immune regulation, Dr. Kirkorian said. Most of her patients with HS are black, and a recent study described a gamma-secretase mutation in a black family of a proband and four family members, she noted (JAMA Dermatol. 2015 Jun;151[6]:668-70). Gamma-secretase mutations also have been identified in Han Chinese populations, she said.

HS has been associated with a range of comorbidities that can make a diagnosis more challenging, Dr. Kirkorian said, pointing out that HS is more likely in patients with Down syndrome and inflammatory bowel disease, as well as insulin resistance. Although data are limited, children with HS are more likely to present with obesity, prediabetes, diabetes, and metabolic syndrome. For these children "multidisciplinary care with endocrinology, nutrition, and weight-loss medicine is critical," Dr. Kirkorian said.

HS also is associated with precocious puberty. However, defining the age of onset of puberty can be difficulty because pubertal onset may vary between different ethnicities, noted Dr. Kirkorian. "Prepubertal children presenting with HS warrant an endocrinologic evaluation," she said.



ELSEVIER

Diagnosis may be delayed as much as 7 years.

Dr. Kirkorian added that more research is needed to pinpoint the possible genetic component of HS and to identify genetic susceptibility that could lead to targeted treatment strategies.

The optimal treatment plan for pediatric HS is multimodal and addresses the comorbidities common with the condition, she said, and she predicted that specialized clinic or treatment centers that bring together areas, including psychiatry, wound care, pain management, surgery, endocrinology, and genetics, will evolve to serve these patients. To support these collaborative efforts, Dr. Kirkorian is a member of the Pediatric Dermatology Research Alliance (PeDRA), an organization formed to accelerate research on skin diseases in children.

The symposium was sponsored by AbbVie. Dr. Kirkorian had no financial conflicts to disclose. She is on the editorial board of Dermatology News.

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COMMENTARY
BY DR. SIDBURY

HIDRADENITIS SUPPURATIVA, like hyperhidrosis, is a condition that can remain hidden. In part due to distribution and in part due to onset around puberty when parents and even pediatricians examine certain areas of skin less often in reticent tweens and teens, delay in diagnosis is the rule.

Dr. Anna Yasmine Kirkorian and her colleagues showed this delay can span 2 years or more in up to 75%; this is an unfortunate statistic for any disease let alone one that is painful and scars so mercilessly. Pediatricians should be alert to telltale signs of "pimples" or "boils" in the folds of the skin, especially in predisposed patients (such as those with Downs syndrome, inflammatory bowel disease, obesity, or metabolic syndrome).

How to decide which 'birthmarks' spell trouble

BY HEIDI SPLETE
REPORTING FROM SDEF WOMEN'S & PEDIATRIC DERMATOLOGY SEMINAR

When evaluating lumps and bumps in infants, categorizing them can help determine whether they need immediate attention, said James R. Treat, MD, a pediatric dermatologist at Children's Hospital of Philadelphia.

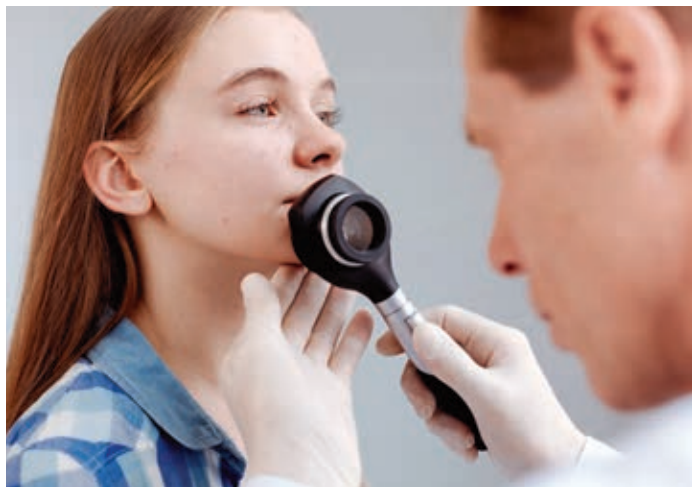
"Divide 'birthmarks' based on appearance, "then decide when to worry," he said in a presentation at Skin Disease Education Foundation's Women's & Pediatric Dermatology Seminar.

For example, Spitz nevi occur in patients younger than 20 years, most often on the face and lower extremities, but most are benign, Dr. Treat said. However, he recommends a biopsy if the patient is pubertal or older, or if the lesions are larger than 8 mm, amelanotic, or show asymmetry, ulceration, or excessive growth.

By contrast, neurocutaneous melanosis is a rare but serious skin condition that occurs in children and can be fatal if it progresses to melanoma, he pointed out. The condition involves the migration of melanocytes into the spinal canal and cerebrospinal fluid during development. Symptoms may include headache, seizures, and paralysis, and clinicians should keep them in mind when seeing children with melanocytic nevi, he noted. The highest risk for melanoma transformation is increased for individuals with more than 20 congenital moles, and "the second-highest risk is having a giant nevus lying overtop of the midline spine or scalp," he said.

In some cases, yellow or tan lesions in children are benign and will resolve on their own, Dr. Treat said.

Juvenile xanthogranuloma, characterized by yellow-brown asymptomatic papules and nodules, develops most often within the first year of life, but the lesions usually resolve spontaneously by school age, he added.



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Mastocytosis, localized collections of mast cells, presents as yellow/tan lesions that develop within the first 2 years of life. The condition can be systemic; patients may experience flushing and diarrhea because of localized release of histamines, and those with a history of weight loss, easy bruising or bleeding, hepatosplenomegaly, or lymphadenopathy may have systemic disease, Dr. Treat explained.

Subcutaneous fat necrosis can present within the first 2 weeks of life as firm, red-purple tender nodules that may be disturbing to parents. These lesions are most likely to appear on the cheeks, arms, back, and thighs, and are related to hypoxia or trauma, he added. The lesions usually resolve spontaneously within a period of weeks to months, although they may heal with some atrophy and scarring, he said. Subcutaneous fat necrosis is associated with hypercalcemia, so "it is important to check frequently, as hypercalcemia can occur weeks after the nodules resolve," he commented.

Dr. Treat disclosed serving as a consultant to Procter & Gamble. SDEF and this news organization are owned by the same parent company.

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COMMENTARY **BY DR. EICHENFIELD**

INFANTILE "LUMPS, BUMPS, AND FLAT MARKS" are quite common, while the set of lesions ranges from common and benign to rare and incredibly severe. Dr. James R. Treat of the Children's Hospital of Philadelphia stresses an approach of categorization and triage, with morphology and diagnosis dictating the "when to worry," as well as the "what to do" and "when to do it."

Large congenital melanocytic nevi with multiple small satellite lesions carry higher risk for neurocutaneous melanosis, as well as melanoma. Isolated congenital melanocytic nevi that are of small or intermediate size have very low risk of melanoma. He stressed that yellow or tan lesions are commonly mastocytomas and juvenile xanthogranulomas, two conditions that can self-resolve over several years, and that both rarely have systemic issues associated with them. Subcutaneous fat necrosis, while not a "birthmark," presents in the first weeks of life as indurated nodules and is commonly seen after "cooling therapy" hypothermia for hypoxic-ischemic encephalopathy. Hypercalcemia can be a problem, both acutely and in the resolving phase, and algorithms for evaluation and follow-up may be useful (Pediatr Dermatol. 2016 Nov;33[6]:e353-5).

Topical anticholinergic drug improved hyperhidrosis in children

BY MITCHEL L. ZOLER
REPORTING FROM AAD 18

SAN DIEGO – A topical anticholinergic drug, glycopyrronium tosylate, was as safe and effective for treating hyperhidrosis in children 9-16 years old as it was in adults in two phase 3 trials that included 25 treated children, raising the prospect it could become the first drug to gain Food and Drug Administration approval for treating pediatric hyperhidrosis.

"Topical glycopyrronium tosylate treatment may provide a much needed treatment option for those with primary axillary hyperhidrosis, including pediatric patients," Adelaide A. Hebert, MD, said at the annual meeting of the American Academy of Dermatology.

The data she reported from a post hoc analysis included 25 children, 9-16 years old, who received a daily, topical application of glycopyrronium tosylate to their underarms for 4 weeks and 19 children treated with vehicle only. The children were enrolled in either of a pair of phase 3 pivotal trials that together randomized 697 patients. In November 2017, Dermira, the company developing this drug, submitted an FDA application for marketing approval of the agent for adults and children at least 9 years old. An FDA decision is expected by mid-2018, according to the company.

Getting approval from the FDA for an effective pediatric hyperhidrosis treatment would be an important advance because nothing now exists in that space, said Dr. Hebert, professor of dermatology and pediatrics and director of pediatric dermatology at the University of Texas Health Sciences Center at Houston.

Based on past FDA actions, safety data from 25 children should be adequate to support pediatric labeling, she said in an interview, though she added that confirmatory safety data from a phase 4 study in children would be a welcome future addition. Hyperhidrosis in adolescents is "underappreciated, underdiagnosed, and is very impactful," and currently has limited treatment options that are readily available for children, especially effective options for more severe hyperhidrosis.

The pediatric data came from the phase 3, randomized, double-blind, vehicle-controlled ATMOS-1 (DRM04 in Subjects With Axillary Hyperhidrosis) trial and the ATMOS-2 trial. The trial ran at several U.S. and German centers, although only the U.S. centers enrolled pediatric patients.

The two trials enrolled patients with "intolerable or barely tolerable" primary, axillary hyperhidrosis of at least 6 months' duration. After 4 weeks, patients treated with glycopyrronium tosylate had improvements in their daily diary account of axillary sweating and in sweat production.

The new pediatric analysis that Dr. Hebert reported showed that the responder rate based on a 4-point or greater improvement in daily sweat diary assessments occurred in 60% of the actively treated children and in 13% of the controls. A 50% or greater reduction in sweat production occurred in 80% of the treated children and in 55% of controls. The treatment was generally well tolerated, with no serious adverse effects reported and with treatment effects that were primarily as expected from an anticholinergic agent, including dry mouth, pupil dilation, and blurred vision.

The ATMOS-1 and ATMOS-2 trials were sponsored by Dermira, the company developing glycopyrronium tosylate. Dr. Hebert has been a consultant to and has received research funding from Dermira, and some of the coauthors of the study are Dermira employees.

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SOURCE: Hebert AA et al. AAD 2018, Abstract 6659.

COMMENTARY
BY DR. SIDBURY

HYPERHIDROSIS is an underappreciated problem in the pediatric population. Primary focal hyperhidrosis can present even in infancy and can have a tremendous impact on quality of life.

The Food and Drug Administration convened a public hearing in the fall of 2017 to hear from stakeholders, including patients. Adult patients told stories of receiving bad grades in school on papers made illegible by sweat stains and smudging. The problem is not merely underrecognition and delay in diagnosis but inadequate treatment options. Currently available interventions include aluminum chloride, which often helps insufficiently or is irritating; systemic anticholinergic agents, which can have intolerable side effects like dry mouth; or botox injections, which are temporary, painful, and expensive.

Dr. Adelaide A. Hebert presents a novel topical anticholinergic agent for axillary hyperhidrosis that is pending approval by the FDA down to 9 years of age. Topical glycopyrronium tosylate showed marked reduction in sweat and improvement in quality of life in the 25 pediatric patients aged 9-16 years. There were no serious adverse effects with only some of the anticholinergic side effects seen from systemic agents. If approved, this would be the first such agent available for patients this age and will meet a tremendous need.

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How to get through the tough talks about alopecia areata with children

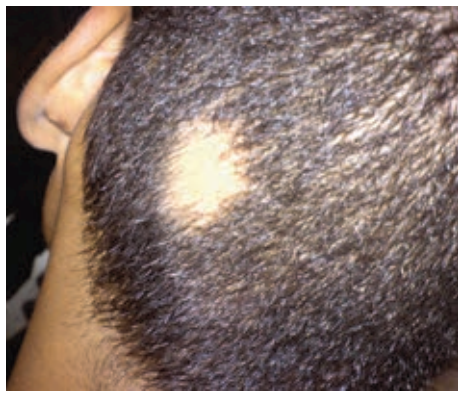
BY KARI OAKES
EXPERT ANALYSIS FROM WCPD 2017

CHICAGO – How do you talk to your alopecia areata patients and their families about hair loss? If you can't set aside the temptation to hurry and take the time to listen, things may not go well, said Neil Prose, MD.

With the caveat that Janus kinase inhibitors show promise, Dr. Prose said that "most children who are destined to lose their hair will probably do so despite all of our best efforts." Figuring out how to engage children and parents and frame a positive conversation about alopecia can present a real challenge, especially in the context of a busy practice, said Dr. Prose, professor of dermatology and medical director of Patterson Place Pediatric Dermatology at Duke University, Durham, N.C.

Drawing on the body of literature addressing effective medical communication and adding what works in his own practice, Dr. Prose offered a framework and concrete suggestions for how to have difficult conversations about alopecia in children.

"These are very culturally specific suggestions, but see which ones work for you," said Dr. Prose, speaking to an international audience at the World Congress of Pediatric Dermatology.



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The last question Dr. Prose asks is, "What other questions do you have?"

Dr. Prose depicted two opposing images. In one, he said, the patient and you are sitting on opposite sides of the table, with the prospect of hair loss looming between them. By contrast, "imagine what it would take to be on the same side of the table, looking at the problem together," he said.

There are many barriers that stand in the way of getting you and the patient on the same side of the issue of dealing with severe alopecia areata. The high emotional content of the discussion can be big factor, not just for the patient and family members but also for you.

"We are often dealing with patient disappointment and, frankly, with our own sense of personal failure" when there isn't always a good set of options, said Dr. Prose. Other specific aspects of severe pediatric alopecia areata that make the conversation difficult include the high degree of uncertainty that any particular treatment will succeed and a knowledge of how to give patients and family members hope without raising expectations unrealistically.

Citing the oft-quoted statistic that, on average, a physician interrupts a patient in the first 17 seconds of the office visit, Dr. Prose said, "Many of us are 'explainaholics,'" spending precious visit time talking about what the physician thinks is important.

Still, it's important to validate parents' concerns and to alleviate guilt. "Patients' families sometimes feel guilty because they are so upset and worried – and it's not cancer," said Dr. Prose. Potential impacts on quality of life are still huge, and all parents want the best for their children, he pointed out.

One way he likes to begin a follow-up visit is simply to ask, "So, how's everyone doing?" This opens the door to allow the child and the family to talk about what's important to them. These may be symptom-related, but social issues also may be what's looming largest.

In order to decipher how hair loss is affecting a particular child, Dr. Prose said he likes to say, "I need to understand how this is affecting you, so we can decide together where to go from here." This gives the family control in setting the agenda and begins the process of bringing you to the same side of the table.

Specific prompts that can help you understand how alopecia is affecting a child can include asking about how things are going at school, what the

CONTINUED ON PAGE 15

COMMENTARY **BY DR. SIDBURY**

ALOPECIA AREATA is a challenging condition on many levels, particularly more severe forms such as alopecia totalis or universalis. We cannot as providers clearly explain cause, predict natural history, or offer definitive treatment. These are difficult messages to give and receive. Confounding this complicated dynamic is the fact that, fortunately, affected patients are typically physically well; the psychological impact on affected patients and their families can be devastating.

Dr. Neil Prose offers advice on navigating these delicate waters that are a blueprint for good doctoring in any chronic condition: Listen, validate, support. Unpredictable circumstances require flexibility and compassion; this approach, so long as it is tempered by hope, will ensure that patients and their families feel they are on a shared journey.

CONTINUED FROM PAGE 14

child's friends know about his or her alopecia, whether there is mocking or bullying occurring, and how the patient, family, and teachers are addressing the global picture.

Parents can be asked whether they are noticing changes in behavior, and it's a good idea to check in on how parents are coping as well, said Dr. Prose.

To ensure that families feel they're being heard and to make sure you are understanding correctly, it's useful to mirror what's been said, beginning with a phrase like, "So, what you're saying is …" Putting a name to the emotions that emerge during the visit also can be useful, using phrases like, "I can imagine that this has been disappointing," or "It feels like everyone is very worried."

But, said Dr. Prose, don't forget about opportunities to praise patients and their families when they've come through a tough time well. This validation is important, he said.

When treatment isn't working, a first place to start is to acknowledge that you, along with the family, wish that things were turning out differently. Then, said Dr. Prose, it can be really important to reappraise treatment goals. After taking the emotional temperature of the room, it may be appropriate to ask, "Is it time to talk about not doing any more treatments?" This question can be put within the framework that hair may or may not regrow spontaneously anyway and that new treatments are emerging that may help in future.

When giving advice or talking about difficult issues, it can be helpful to ask permission, said Dr. Prose. He likes to begin with, "Would it be okay if I ...?" Then, he said, the door can be opened to give advice about school issues, to ask about difficult treatment decisions, or even to share tips learned from other families' coping methods.

The very last question Dr. Prose asks during a visit is "What other questions do you have?" The question is always framed exactly like this, he said, because it assumes there will be more questions, and it gives families permission to ask more. Although most of the time there aren't any further questions, Dr. Prose said, "Do not ask the question with your hand on the doorknob!"

Dr. Prose had no relevant financial disclosures.

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Teen tanning bed bans keep patients from phototherapy

BY CATHERINE COOPER NELLIST
FROM CLINICS IN DERMATOLOGY

Bans keeping minors from using commercial tanning beds may be depriving dermatology patients of an alternative way to access phototherapy, said Daniel J. Lewis and Madeleine Duvic, MD, of the University of Texas MD Anderson Cancer Center, Houston.

To prevent skin cancer, many states and the District of Columbia have set in place age restrictions on the use of commercial tanning beds and banned minors from indoor tanning; another 12 states put in place bans at younger ages. The Food and Drug Administration proposed a policy in 2015 that would keep all minors from indoor tanning, according to Mr. Lewis and Dr. Duvic.

Phototherapy is known to be an effective treatment for psoriasis, mycosis fungoides, and vitiligo. Phototherapy usually is given in physician offices and administered in ultraviolet B for treatment of psoriasis, but studies have found that tanning beds, which emit primarily ultraviolet A, can produce a clinical response in 80% of psoriasis patients, and 53% of patients report using tanning beds for psoriasis treatment, Mr. Lewis and Dr. Duvic said in a letter to the editor in Clinics in Dermatology.

Despite the risks, making tanning beds "uniformly illegal for minors would be a disservice to patients with limited access to phototherapy. A more effective approach might be to collaborate with the tanning industry to achieve reasonable limits on age and exposure as opposed to an outright ban. At the very least, patients who receive a prescription from a dermatologist should be exempted from a universal ban," they concluded.

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SOURCE: Lewis, DJ and Duvic, M. Clin Dermatol. 2018 Jan-Feb;36(1):104-5

COMMENTARY
BY DR. SIDBURY

EVEN WELL-INTENDED public health initiatives can have unintended consequences. Many states have taken steps to limit the use of tanning beds by underage patients in an effort to prevent skin cancer.

Investigators at the University of Texas MD Anderson Cancer Center, Houston, remind us that phototherapy for conditions such as psoriasis, vitiligo, and even cutaneous T-cell lymphoma do not always occur in doctor's offices. Although commercial tanning beds are less regulated and more chromatically constrained (tanning beds emit very little UVB radiation), they are, for most, cheaper and more accessible. A typical phototherapy schedule requires treatments two to three times weekly for months, so this is not a trivial concern. As more states rightly consider how to sensibly protect children from a known carcinogen, ultraviolet light, they would do well to consider therapeutic exceptions.

Central centrifugal cicatricial alopecia can occur in adolescents

BY ELI ZIMMERMAN
FROM PEDIATRIC DERMATOLOGY

Central centrifugal cicatricial alopecia (CCCA) can affect adolescents, and a study of six biopsy-proven cases indicates CCCA has a genetic component, Ariana N. Eginli and her colleagues report in Pediatric Dermatology.

CCCA, a scarring alopecia that disproportionately affects middle-aged women of African descent, has been attributed to hair care and styling practices.

In this series, however, five of the six patients had a maternal history of CCCA, and only one had used chemical products or styling tools. "Specifically, the early onset of CCCA in these patients with natural virgin hair raises the possibility of genetic anticipation," wrote Ms. Eginli of Wake Forest Baptist Health, Winston-Salem, N.C., and her coauthors. "Therefore, recognizing that CCCA can present in children, particularly in those with a positive family history, is of utmost importance in controlling further disease progression and improving their quality of life."

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"THE EARLY ONSET OF CCCA IN THESE PATIENTS WITH NATURAL VIRGIN HAIR RAISES THE POSSIBILITY OF GENETIC ANTICIPATION."

The authors described four patients treated at the Hair Disorder Clinic at Wake Forest and two treated between 2012 and 2015 at the Nelson R. Mandela School of Medicine in Durban, South Africa. Tender scalp papules, pruritus, and scaling of the scalp were among the presenting symptoms, in addition to hair loss. Histology confirmed CCCA in all six patients, who were diagnosed at ages 14-19 years. Five of the six patients had a family history of CCCA. Family history was not known for the sixth adolescent, who was adopted.

Two patients had previously undergone scalp surgery, specifically ventriculoperitoneal shunt placement, years before their hair loss began. The authors speculated that the scalp surgery may have contributed to the early development of CCCA.

"We recommend that clinicians check for early signs of CCCA when there are complaints of hair loss on the scalp of offspring of affected women of African descent," they wrote. "If there is any clinical suspicion of CCCA or any scarring alopecia, a scalp biopsy should be performed."

Ms. Eginli had no disclosures. One of her colleagues is a consultant for and has received grant support from various drug companies.

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SOURCE: Eginli AN et al. Pediatr Dermatol. 2017 Mar;34[2]:133-7.

COMMENTARY **BY DR. SIDBURY**

CENTRAL CENTRIFUGAL CICATRICIAL ALOPECIA (CCCA) is a type of scarring alopecia typically seen in middle-aged women of African descent with a history of exposure to certain hair care practices (such as tight braids, hot combs). It is very rare in the pediatric population. Ariana N. Eginli and her colleagues describe biopsy-proven CCCA in six patients aged 14-19 years at referral centers in North Carolina and South Africa. A positive family history was noted in all of the patients (5/5) in whom this information was available.

Only one patient had used any styling products. Pediatricians encountering at-risk patients with characteristic features of tender papules, scaling, pruritus, and alopecia may use a family history to consider this diagnosis before telltale scarring occurs. Counseling regarding certain hair care practices such as hot combs and straighteners can potentially prevent unnecessary exacerbation. Early referral for skin biopsy and long term management may lead to better outcomes.

Consider different *Tinea capitis* presentations in children with hair loss

BY HEIDI SPLETE
REPORTING FROM SDEF WOMEN'S & PEDIATRIC DERMATOLOGY SEMINAR

Categorizing hair loss in children depends on many factors, but it is important to rule out an infectious etiology as early as possible, according to Sheila Fallon Friedlander, MD.

"What can *Tinea capitis* look like? Anything," she said in a presentation at Skin Disease Education Foundation's Women's & Pediatric Dermatology Seminar.

Although *T. capitis* most often presents in children aged 3-7 years as a pattern of localized hair loss, often with scaling, sometimes with nodules, other possibilities include pustules, boggy masses, and diffuse hair loss, said Dr. Friedlander, professor of pediatrics and dermatology at the University of California, San Diego.

Sometimes, the hair loss may be so subtle that families come in complaining of "dandruff" rather than hair loss, she noted. Evaluating the patient for the presence of cervical or occipital lymph nodes is crucial; big nodes are usually a tip-off that infection is present.

The prevalence and etiology of tinea remains a moving target, and *T. capitis* varies with place and time, Dr. Friedlander observed. Historically, *T. capitis* has been most common in inner-city communities and developing countries, but "change is in the air," she said, citing recent epidemiologic data from countries including Egypt, Palestine, Kuwait, Tunisia, and Saudi Arabia showing *Microsporum canis* overtaking *Trichophyton violaceum* as the dominant organism causing *T. capitis*. The upswing in *M. canis* traces back to family pets, especially cats and dogs, but "don't forget hamsters," she said.

Clinicians treating *T. capitis* should ask about family pets, advised Dr. Friedlander, adding that city dwellers' conditions may be more likely caused by *T. tonsurans*, *T. violaceum*, or *T. soudanense*. Also consider immigration status and family history when evaluating *T. capitis*, and use a Wood's lamp for diagnosis if one is available, she advised. *M. canis* will fluoresce and *T. tonsurans* will not, she pointed out.

Other strategies to evaluate the condition include KOH, culture, polymerase chain reaction, and trichoscopy.

The optimal treatment plan for *T. capitis* depends on the source, Dr. Friedlander explained. If *M. canis* is the cause, "griseofulvin is the drug of choice," along with a twice-weekly spermicidal shampoo, she said.

Other treatment options include terbinafine, itraconazole, and fluconazole, and each have their pros and cons, she said. Terbinafine – which persists for months in the skin, nails, and hair – is the least expensive, and is her first choice for infections caused by *T. tonsurans*.

Itraconazole is available as a liquid, but costs more, causes diarrhea, and comes with a boxed warning about the potential for cardiac complications; fluconazole is the most expensive, but may be used in infants, she added.

Other high-risk groups for *T. capitis* include female caretakers of high-risk individuals, such as "grandma"; wrestlers; and Buddhist monks, she said. "Short hair, sharing combs, and unclean barbers" contributed to a documented increased risk of *T. capitis* according to a recently published study of 60 Buddhist monks whose average age was 11.6 years, she added. (Pediatr Dermatol. 2017 May;34[3]:371-3).

Dr. Friedlander had no relevant financial conflicts to disclose.

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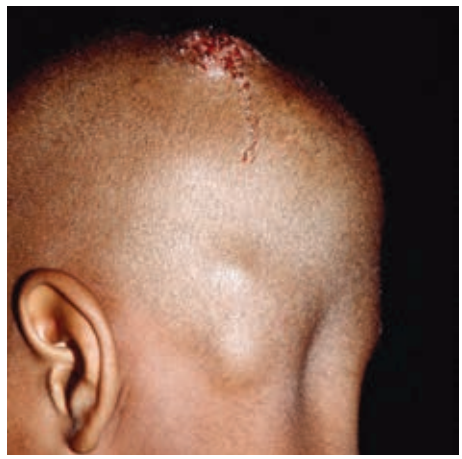

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"What can Tinea capitis *look like? Anything," said Dr. Sheila Fallon Friedlander.*

COMMENTARY
BY DR. SIDBURY

TINEA CAPITIS can look like "anything," according to Dr. Sheila Friedlander. Three of the four cardinal signs can be seen in common inflammatory mimics such as psoriasis or seborrheic dermatitis: alopecia, erythema, and scaling. The fourth, lymphadenopathy, while not specific, is more suggestive of an infectious process. Bedside diagnostic tools like a KOH (potassium hydroxide) exam can confirm diagnosis, but speciation requires tests like fungal culture, which will take as long as a month.

Dr. Friedlander advises that a history and Wood's light exam can offer earlier clues. Pet ownership – including dogs, cats, and even hamsters – might suggest *Microsporum canis* infection as would fluorescence with a Wood's light. This matters, according to Dr. Friedlander, as griseofulvin is her first-line choice for *M. canis* infections, whereas for *Trichophyton* infections, she prefers terbinafine.

There are many aspects to caring for epidermolysis bullosa patients

BY DOUG BRUNK
AT WCPD 2017

CHICAGO – Ask patients with recessive dystrophic epidermolysis bullosa (EB) to name their most bothersome symptom, and they're likely to say itch, followed closely by pain, according to Jemima Mellerio, MD.

"We don't really understand a lot about the mechanism of itch in patients with this disease, which is one of the reasons why we don't have good treatments," Prof. Mellerio said at the World Congress of Pediatric Dermatology.

No magic cure exists, but options to try include topical measures such as emollients, menthol, bandages, and topical steroids; antihistamines; antidepressants, such as amitriptyline and doxepin; anticonvulsants, such as gabapentin; and serotonin inhibitors, such as ondansetron. There have also been case reports of benefits with thalidomide, cyclosporine, and methotrexate, "but you need to be careful because it's very difficult to monitor for the peripheral neuropathy that you can get with thalidomide if you have epidermolysis bullosa," said Prof. Mellerio, a dermatologist at St. John's Institute of Dermatology and Great Ormond Street Hospital, England. "If you have a type of EB that predisposes you to malignancy, using cyclosporine is a concern."


DR. MELLERIO

A key resource for patients with EB and clinicians who care for them is DEBRA International, a network of national groups working on behalf of people with EB, which is undertaking a long-term initiative to develop clinical practice guidelines for the disorder. "This has been going on for about 5 years and is gathering momentum," Prof. Mellerio said. "In the EB literature, there is very little that is good-quality, evidence-based medicine." Links to existing guidelines can be accessed DEBRA website.

She shared clinical tips for managing various aspects of EB, including pain, which was the subject of a recent 23-page clinical practice guideline (BMC Med. 2014;12:178). "It's important to take a proper history: What kind of pain is it and when do they get it?" she commented. "Is there anything that is triggering it?" Basic treatment principles are to start with simple options like acetaminophen/NSAIDs and add in weak opiates as appropriate. Go a bit stronger if necessary, titrating to get the desired effect. "If you have specialist pain services, that can be extremely useful in some of the more complex cases," she said.

Many EB patients are plagued by neuropathic pain that burns and stings. "For these cases, you might try tricyclic antidepressants or anticonvulsants like gabapentin and pregabalin," she noted. Anxiolytics such as midazolam can be used to reduce anxiety during procedures, bathing, and dressings. A wide range of pain formulations exist to meet patient needs or preferences, including oral tablets or suspensions, lozenges, intranasal preparations, transdermal patches, and intramuscular and intravenous injections.

Topical measures for isolated, painful wounds include ibuprofen-impregnated dressings such as Biatain Ibu and topical morphine gel. "You can get this made up by using morphine sulfate and mixing it in a hydrogel," Prof. Mellerio said. "You apply that when you have a limited number of painful wounds, so you don't get the systemic effects from having morphine but you get the local beneficial effects." [This approach was described in Arch Dis Child. 2004;89:679-81.] Adding salt to a bath can also ameliorate pain for patients. She recommends adding 90g of salt to 10L bath water for a 0.9% solution, which translates into about 800g salt for a half-full tub of water.

Basic skin care is another challenge for EB patients. For those with extremely fragile skin, Prof. Mellerio recommends applying a primary layer of a soft silicone or lipidocolloid dressing under a secondary dressing layer. "There's a whole range of soft silicone foam

CONTINUED ON PAGE 21

COMMENTARY **BY DR. SIDBURY**

IT ALWAYS HAS SEEMED diabolical that a disease of cutaneous fragility like epidermolysis bullosa (EB) also would be notoriously itchy. Professor Jemima Mellerio discussed some of the primary challenges facing EB patients including itch, pain, and infection, and oral and bone health. For pediatricians not accustomed to caring for EB patients, there are helpful guidelines available online. Certainly most EB patients will require multidisciplinary specialist care including dermatology, otolaryngology, dental, gastroenterology, and nutrition to name several; but the nature and chronicity of EB will require that the pediatricians ideally play the role of quarterback, and the more regular care needs they can meet, the better for patient and family.

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Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

In three Phase 3 clinical trials, 616 subjects were exposed to LUZU Cream, 1%: 305 with interdigital tinea pedis and 311 subjects with tinea cruris. Subjects with interdigital tinea pedis or tinea cruris applied LUZU Cream, 1% or vehicle cream once daily for 14 days or 7 days, respectively, to affected and adjacent areas. During clinical trials with LUZU Cream, 1% the most common adverse reactions were application site reactions which occurred in less than 1% of subjects in both the LUZU and vehicle arms. Most adverse reactions were mild in severity.

A post-approval clinical trial was conducted in 75 subjects age 2 to <18 years old with tinea corporis. The adverse reactions in the LUZU Cream, 1% treated population were similar to the vehicle treated population.

Postmarketing Experience
The following adverse reactions have been identified during postmarketing use of luliconazole cream, 1%: contact dermatitis and cellulitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS
An in vivo study in adult subjects with moderate to severe interdigital tinea pedis and tinea cruris showed that LUZU Cream, 1% is a weak inhibitor of CYP2C19. In a separate trial in adolescent subjects with tinea cruris, in vivo blood levels of LUZU Cream, 1%, were seen to approach those levels sufficient to show moderate inhibition of CYP2C19. *[see Clinical Pharmacology in full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary
There are no available data with LUZU Cream, 1% use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies with pregnant rats and rabbits, there were no adverse developmental effects observed with subcutaneous administration of luliconazole during organogenesis at doses up to 3 and 24 times, respectively, the maximum recommended human dose (MRHD) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data
Animal Data
The animal multiples of human exposure calculations were based on daily dose body surface area (BSA) comparisons (mg/m^2) for the reproductive toxicology studies described in this section and in *Carcinogenesis*, *Mutagenesis, Impairment of Fertility*. The maximum recommended human dose (MRHD) was set at 8 g 1% cream per day (1.33 mg/kg/day for a 60 kg individual, which is equivalent to 49.2 mg/m^2/day).

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 7-17) to pregnant female rats. No treatment-related effects on maternal toxicity or malformations were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons). Increased incidences of skeletal variation (14^{th} rib) were noted at 25 mg/kg/day. No treatment-related effects on skeletal variation were noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons).

Subcutaneous doses of 4, 20 and 100 mg/kg/day luliconazole were administered during the period of organogenesis (gestational days 6-18) to pregnant female rabbits. No treatment-related effects on maternal toxicity, embryofetal toxicity or malformations were noted at 100 mg/kg/day (24 times the MRHD based on BSA comparisons).

In a pre- and postnatal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered from the beginning of organogenesis (gestation day 7) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (0.6 times the MRHD based on BSA comparisons). No treatment effects on postnatal development were noted at 25 mg/kg/day (3 times the MRHD based on BSA comparisons).

Lactation
Risk Summary
There is no information available on the presence of luliconazole in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production after topical application of LUZU Cream, 1% to women who are breastfeeding. LUZU Cream, 1% has low systemic absorption. The lack of clinical data during lactation precludes a clear determination of the risk of LUZU Cream, 1% to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUZU Cream, 1% and any potential adverse effects on the breastfed infant from LUZU Cream, 1% or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of LUZU Cream, 1% in pediatric patients 12 to <18 years of age with tinea pedis and tinea cruris have been established by evidence from well-controlled trials in adult and pediatric subjects and a pharmacokinetic (PK) study in pediatric subjects *[see Clinical Pharmacology and Clinical Studies in full Prescribing Information]*.

The safety and effectiveness of LUZU Cream, 1% in pediatric patients 2 to <18 years of age with tinea corporis have been established by evidence from a well-controlled trial in pediatric subjects *[see Clinical Pharmacology and Clinical Studies in full Prescribing Information]*.

Geriatric Use
Of the total number of subjects in clinical studies of LUZU Cream, 1%, 8 percent were 65 and over, while 1.4 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies to evaluate the carcinogenic potential of LUZU Cream, 1% have not been conducted.

Luliconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames assay and Chinese hamster lung cell chromosomal aberration assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus test).

In a fertility study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day luliconazole were administered prior to and during mating and through early pregnancy. Treatment related effects on reproductive function were noted in females (decreased live embryos and decreased corpus luteum) at 5 and 25 mg/kg/day and males (decreased sperm counts) at 25 mg/kg/day. No treatment related effects on fertility or reproductive function were noted at 1 mg/kg/day (0.1X MRHD based on BSA comparisons).

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information)

Inform patients that LUZU Cream, 1% is for topical use only. LUZU Cream, 1% is not intended for intravaginal or ophthalmic use.

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by: Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada

Rev 03/2018
Based on 9438802

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Multimodal approach is state of the art for ulcerated infantile hemangiomas

BY KARI OAKES
EXPERT ANALYSIS FROM WCPD 2017

CHICAGO – When an infantile hemangioma begins to ulcerate, a multimodal approach has the best chance of controlling bleeding, preventing infection, and achieving the dual goals of volume reduction and resolution of the ulcer.

About 16% of infantile hemangiomas become ulcerated at some point during their proliferative phase, said Kate Puttgen, MD, during a talk at the World Congress of Pediatric Dermatology.

Hemangiomas are more likely to ulcerate if they are large, superficial, or segmented; if they're located in an intertriginous area or are on the mucosa; or if they are of a mixed subtype, said Dr. Puttgen. Patient factors that may increase risk for ulceration include prematurity, low birth weight, and being female.

AN ULCERATED IH NEEDS WOUND CARE WITH BARRIER CREAMS AND DRESSINGS.

One clinical clue to picking up an infantile hemangioma (IH) that's destined to ulcerate is an early grayish to white discoloration of the lesion, said Dr. Puttgen, chief of the division of pediatric dermatology at Johns Hopkins Medicine, Baltimore.

"Multimodal therapy is an absolute necessity" in treating an ulcerated IH, said Dr. Puttgen. Using an "all hands on deck" approach – a combination of topical and systemic modalities – can help bring the lesion under control.

Beta-blockers are first-line therapy to manage complicated IHs, with propranolol yielding a 98% response rate for all complicated IHs in the literature, said Dr. Puttgen.

Propranolol can decrease the volume and color of IHs and speed

CONTINUED ON PAGE 22

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dressings or polymeric membrane, which is a nice soft dressing that can go over a primary dressing or directly on the skin if fragility is not a problem," she said. "Really, it comes down to patient and [cargiver] choice as to what to use. It depends on many factors including site, exudate, pain, and dressing size. The frequency of wound changes will also vary. So, if you've got an infected, more heavily exuding wound, the dressing changes will be more frequent."

Critical colonization and infection are significant problems for EB patients and are ideally managed with topical antimicrobials such as hydrogen peroxide cream, enzymatic antimicrobials, polyhexamethylene biguanide, and medical grade honey. "Topical antibiotics such as mupirocin can also be used, but there are problems with resistance if you're using it long term and potential for sensitization," Prof. Mellerio said. "Other options include antimicrobial dressings such as polymeric membrane, polyhexamethylene biguanide, and silver. With silver dressings, there is the potential to absorb silver, so, if you're a child and you have a lot of wounds on your skin, you can absorb silver at significant levels, which could be a problem."

If patients don't respond to topical measures, consider using oral antibiotics for 10-14 days, she said. Swab first for sensitivity and to look for streptococcal carriage "because you can get a lot of problems like renal damage," and use IV antibiotics only for severe infections, she said. "Best Practice Guidelines for Skin and Wound Care in Epidermolysis Bullosa," supported by an award from the Urgo Foundation and produced by Wounds International/Wounds UK, are available.

Prof. Mellerio noted that EB can also adversely affect oral health and lead to the formation of painful blisters, scarring, microstomia, and ankyloglossia, which "can contribute to difficulties eating and speaking and make it hard to keep the teeth clean." Analgesics can be helpful, as can an NSAID mouthwash or spray or mucoprotectants like Episil that coat the surface of lesions. "Alcohol-free chlorhexidine washes and fluoride mouth washes can help, as can high fluoride toothpaste and trying to limit the consumption of sugary foods and snacks," she said. "You can adapt things like toothbrushes with a grip, which means that it's a bit easier for somebody with EB to be able to keep their teeth clean."

Keeping bones strong also is a concern, since osteopenia and osteoporosis are common in EB. "We've seen vertebral crush fractures in children as young as 5 years old," Prof. Mellerio said. "Optimize calcium and vitamin D and mobility, which is important in helping people accrue their bone mineral density throughout life. Sometimes, we have to use bisphosphonate therapies, but there isn't a great deal in the literature to support what the best way of doing this is."

Prof. Mellerio reported having no financial disclosures.

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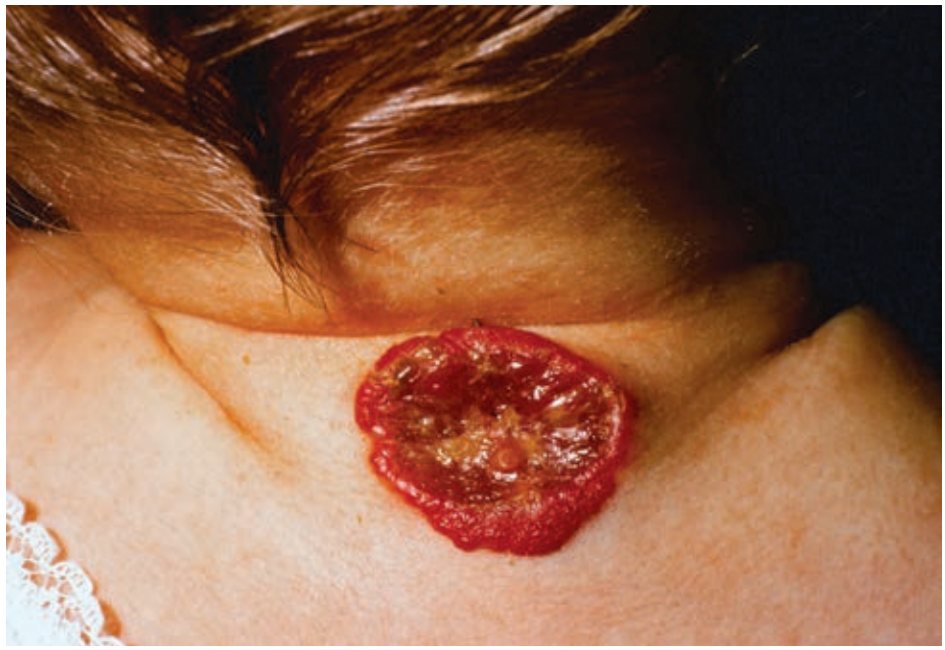
CONTINUED FROM PAGE 21

involution, in part by its ability to continue working after the proliferative growth phase of an IH. It's also been shown to reduce the need for surgery in nasal IH, and it's well tolerated, she added.

Evidence-based therapies for ulcerated hemangiomas include systemic propranolol at 1-3 mg/kg per day. That protocol will result in a healed ulcer within 2-6 weeks in most of the published case series, Dr. Puttgen noted.

Topical timolol also has evidence supporting its use for an ulcerated IH, and it has been found generally safe. In one study of 30 patients with IH, she said, three had mild adverse events consisting of sleep disturbance, diarrhea, and acrocyanosis. Another study reported success when brimonidine 0.2% and timolol 0.5% were used together. It's possible, said Dr. Puttgen, that there's a synergistic effect when combining the selective alpha-2 adrenergic agonist effect of brimonidine with timolol, which provides nonselective beta adrenergic blockade. However, she said, there has been an isolated report of brimonidine toxicity.

An ulcerated IH needs wound care, Dr. Puttgen added, with barrier creams and dressings. Pain management should be considered, because an ulcerated IH may have a large, friable, bleeding area. Pulsed-dye laser also can be a useful treatment modality for an ulcerating IH.



COURTESY DR. MICHAEL O. MURPHY

About 16% of infantile hemangiomas become ulcerated at some point during their proliferative phase.

Going beyond the treatments for which the evidence is strongest and moving into more "state-of-the-art" treatments, "there may be a niche role for oral corticosteroids" as combination systemic therapy with propranolol, Dr. Puttgen said.

She shared images from a recently published report, in which she's the senior author, showing the progression of an ulcerated IH. The hemangioma had received wound care and pulsed-dye laser treatment, and the infant was started on systemic propranolol. After 2 weeks, the IH had decreased significantly in volume, but the ulcerated area had actually increased. With the addition of oral corticosteroids, there was a reduction in ulceration after 2 weeks; and after 5 weeks of prednisolone, "the ulceration resolved without rebound," said Dr. Puttgen. The corticosteroid was then tapered and propranolol was continued for an additional 2 months, then tapered. By 10 months, the IH had almost completely resolved (Br J Dermatol. 2017 Apr;176[4]:1064-7).

If a corticosteroid is added to propranolol, there may be benefit to a slower propranolol dose, Dr. Puttgen said. She suggests an altered dosing schedule, beginning with 1 mg/kg per day in two or three divided doses. Then, over a period of 2-7 days, the total daily dose can be increased to 1.5 mg/kg per day. Bumping the dose up to 2 mg/kg per day or higher should not happen until after 2 weeks at the reduced dosing schedule, she explained.

Dr. Puttgen disclosed that she is on the advisory board and has received honoraria from Pierre Fabre Dermatologie.

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COMMENTARY **BY DR. EICHENFIELD**

ULCERATIVE HEMANGIOMAS can be very challenging, and having a vascular lesion with open erosions, bleeding, infection, and/or pain can be anxiety provoking for parents and health care practitioners. These are estimated to occur in 16% of hemangiomas, and the article discussing the approach of Dr. Kate Puttgen of Johns Hopkins Medicine stresses that multimodal therapy often is required to manage them. Oral propranolol is usually the "go-to" agent because the evidence basis for clinical response is best for it. Other therapies include topical timolol, local care with barrier creams, dressings, pain management, pulsed dye laser, and even oral corticosteroids. The desire is to heal the ulcerated areas as soon as possible while trying to minimize the extension of the ulceration, and often this requires a "master chef" approach to utilizing the therapies for the best results.

Systemic corticosteroids not recommended for long-term treatment of atopic dermatitis

BY IAN LACY

FROM THE JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

Systemic corticosteroids (SCSs) should be limited to short courses as a transition to steroid-sparing therapies in patients with atopic dermatitis because of the potential for adverse effects, reported Sherry Yu, MD, of Massachusetts General Hospital, Boston, and her associates.

Rebound flares are one of many adverse effects (AEs) that can occur when using SCSs, according to a systematic review of 52 reviews and 12 studies. Several of the studies from the systematic review found that rebound flares occurred after discontinuation of oral prednisone. One such study found that 15 of 38 patients (40%) with severe atopic dermatitis (AD) had to discontinue use of oral prednisone because of disease flares. Another study comparing oral vs. intramuscular methylprednisolone found that patients experienced rebound flares 1 week after discontinuing use of SCSs; in this particular study, there was no long lasting improvement in patients' AD, Dr. Yu and her associates said.

Another AE is adrenal insufficiency, defined as a cortisol level less than or equal to 500 nmol/L. In a meta-analysis of 74 articles with 3,753 participants, there was a significant increase in absolute risk of adrenal insufficiency with medium-term use (1 month to less than 1 year) and long-term use (more than 1 year) of SCSs, as well as medium and high doses of SCSs. Adrenal insufficiency can occur in as little as 4 weeks and may be subclinical. This can leave patients vulnerable to infection. Adrenal insufficiency also can manifest itself as weakness, fatigue, and shock in more severe cases.

Dr. Yu and her colleagues noted that tapering may minimize the risk of adrenal insufficiency and that a single morning dose or alternate dosing strategy may minimize this risk.

Another finding from this study was the adverse effects the SCSs have on pediatric patients. One study showed that 7 of 10 (70%) of children taking maintenance doses of beclomethasone dipropionate had growth impairment after 6 months of therapy. Significant growth disruption also was observed in children who had taken beclomethasone dipropionate only 4 weeks.

Dr. Yu and her colleagues warned that SCS should not be used to treat pediatric AD "because of growth retardation and other AEs."

Dr. Yu reported no relevant financial disclosures. The other three authors reported relationships with various companies in the industry.

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SOURCE: Yu S et al. J Am Acad Dermatol. 2017 Oct 13. doi: 10.1016/j.jaad.2017.09.074.

COMMENTARY **BY DR. EICHENFIELD**

THERE CONTINUES TO BE a large amount of research into atopic dermatitis (AD), and multiple topical and systemic agents are being studied for pediatric and adult AD. Some useful epidemiologic work has shown that it may have been too simplistic a perspective to think that AD in childhood always presents in early life and resolves within a few years. While about 15% of AD patients in a large English cohort study and Dutch birth cohort study (with more than 18,000 children) followed this pattern, a significant percentage had early onset with late resolution or early onset with persistence. In addition, some later-onset AD occurred, more commonly associated with asthma. The most important takeaway was that AD exists in a variety of forms – with variations in onset, persistence, severity, timing of changes or resolution, and associated comorbidities.

Understanding the effects of AD and its secondary consequences has definitely fueled a desire to more adequately control the disease and to push a "long-term disease control" model rather than episodic treatment of flares without good, proactive maintenance regimens. Systemic corticosteroids remain a troublesome treatment for AD, as discussed in the article by Dr. Sherry Yu of Massachusetts General Hospital. Systemic side effects, adrenal insufficiency, growth impairment, and rebound flares all are reasons to avoid relying on systemic corticosteroids.

Ongoing therapeutic trials for systemic agents in children and adolescents include the testing of biologic agents – such as dupilumab, interleukin-4 and interleukin-13 blockers, and JAK inhibitors – that target cytokine pathways important in AD. Studies have been published recently on the already-approved topical phosphodiesterase-4 inhibitor crisaborole, including a 1-year safety study. Work on other topical agents, such as the aryl hydrocarbon receptor mediator tapinarof, continues; this work was highlighted in the article relating the presentation of Johnny Peppers, PhD, at the congress of the European Academy of Dermatology and Venereology meeting. This agent may work through inhibiting proinflammatory mediators including interleukin-6 and interleukin-17A. The topical 1% cream is being studied for both AD and psoriasis.

Large Dutch study: Atopic dermatitis subphenotypes are identified in children

BY CATHERINE COOPER NELLIST
FROM THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Identification of subphenotypes of atopic dermatitis (AD) in children, with differing risk factors, prognoses, and comorbidities, could lead to a stratified approach to managing pediatric AD, said Lavinia Paternoster, PhD, of the University of Bristol, England, and her associates.

Mothers completed questionnaires about an itchy rash and other factors associated with atopic dermatitis (AD) both in an English birth cohort study of 14,701 children aged 6 months to 16.5 years and in a Dutch multicenter birth cohort of 3,963 children aged 3 months to 11 years. DNA tests determined whether the children had filaggrin (FLG) gene mutations and other genotypes associated with AD risk. To determine heterogeneity in patterns of AD, longitudinal latent class analysis was used.

The study identified six classes of AD in these children. Early-onset/early-resolving AD, occurring in 13%-15% of the children, was most prevalent and was associated with male gender. Children in this class had a favorable prognosis, and there was only a very weak association with asthma in later life.

Two classes of persistent disease were identified: early-onset persistent AD (rash occurring in most of this class by 30 months and resolving in half by 16.5 years) and early-onset/late-resolving AD (rash occurring in most by 30 months and resolving in most by 16.5 years). These classes, occurring in about 7% of the children, had the strongest association with an AD genetic risk score; a strong link with personal and parental history of atopic disease; and a strong tie to asthma.

An unrecognized class of mid-onset–resolving AD, occurring in 7% of children, was not significantly linked to FLG mutations but was tied to asthma. In those children, AD prevalence rose sharply from 2.5 years of age and peaked at about 6 years, Dr. Paternoster and her associates said.

The investigators also found an unaffected/transient AD class in which children either had never reported rash; had one or two isolated occasions of rash; or reported a rash consistent with AD at 6-18 months that declined with age. In the two cohorts, 58%-63% children fell into this class. Late-onset–resolving AD occurred in 7%-8% of children, with most developing rash by 12 years and declining by 16.5 years.

"THERE WAS EVIDENCE THAT FLG NULL MUTATIONS WERE ASSOCIATED WITH ALL CLASSES."

There was a preponderance of females in the early-onset persistent AD and the late onset classes, and more males in the early-onset–resolving class. "The associations with asthma at ages 7 and 11-13 years were strongest with the persistent class, but all AD classes showed evidence of some increased risk of asthma at these ages," the researchers wrote.

"There was evidence that FLG null mutations were associated with all classes, however ... the association was strongest in the group with early-onset-persistent disease," the researchers said. The "heterogeneity of effect of genetic variants on different disease profiles, emphasizes the need for patient stratification in future genetic studies. Stratification may be used to increase the power to detect variants associated with specific classes; stratification could also allow the identification of phenotype-specific mechanistic pathways as future therapeutic targets."

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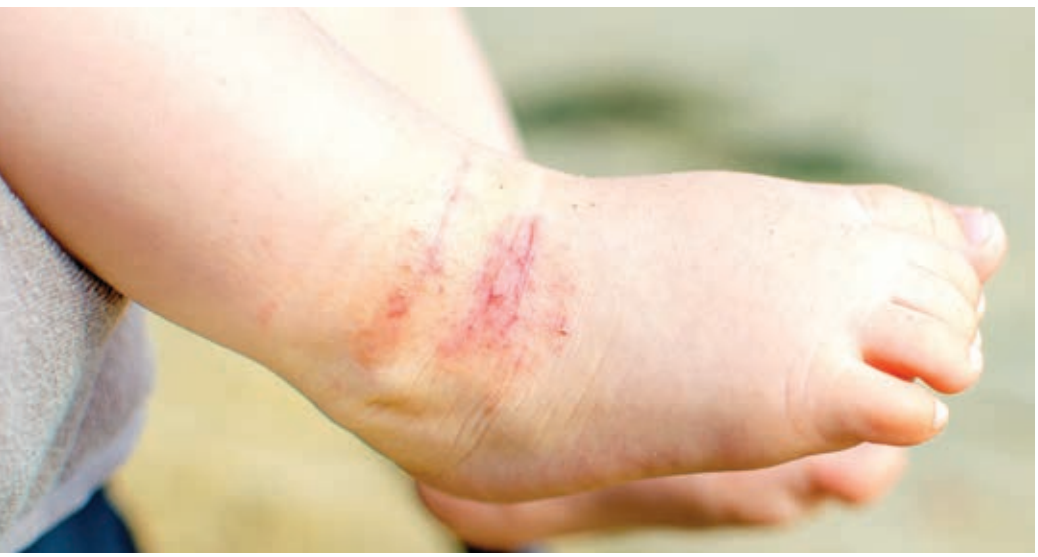


LUCALORENZELLI/THINKSTOCK

An unrecognized class of mid-onset–resolving AD was tied to asthma.

SOURCE: Paternoster L et al. J Allerg Clin Immunol. 2017 Nov 10. doi: 10.1016/j.jaci.2017.09.044.

Topical tapinarof heads for phase 3 trials in atopic dermatitis and psoriasis

BY BRUCE JANCIN
REPORTING FROM THE EADV CONGRESS

GENEVA – Tapinarof cream, a first-in-class topical nonsteroidal anti-inflammatory agent, successfully met its primary and secondary efficacy endpoints in a large international, phase 2, dose-ranging study and is moving on to a phase 3 trial for atopic dermatitis.

Tapinarof is a naturally derived compound whose therapeutic mechanism of action has recently been shown to involve activation of the aryl hydrocarbon receptor, Johnny Peppers, PhD, said at the annual congress of the European Academy of Dermatology and Venereology.

This first-in-class agonist of the aryl hydrocarbon receptor was further shown in both mouse models and in vitro human skin studies to inhibit specific proinflammatory mediators, including interleukin-6 and interleukin-17A, and enhance skin barrier function (J Invest Dermatol. 2017 Oct;137[10]:2110-9), said Dr. Peppers, director of clinical development at GlaxoSmithKline in Research Triangle Park, N.C.

GlaxoSmithKline also is developing tapinarof cream for mild to moderate plaque psoriasis, a disease that hasn't seen a novel nonsteroidal topical therapy approved in more than 25 years. After a strong showing in a phase 2 study, a phase 3 trial in psoriasis is now scheduled.

Dr. Peppers presented a phase 2, double-blind, vehicle-controlled randomized trial including 247 adolescent and adult patients with mild, moderate, or severe atopic dermatitis. The six study arms were tapinarof cream at 1% or 0.5% or vehicle, self-administered at a frequency of either once or twice daily. Participants had a mean baseline Investigator's Global Assessment (IGA) score of 3.1 on a 5-point scale, an Eczema Area and Severity Index (EASI) score of 9.8-13.1 in the various study arms, and a 5.1-5.8 score on an 11-point self-rated itch severity score recorded weekly.

"The 1% tapinarof arm showed higher efficacy and had a quicker onset of action than the 0.5% arm or vehicle," he reported.

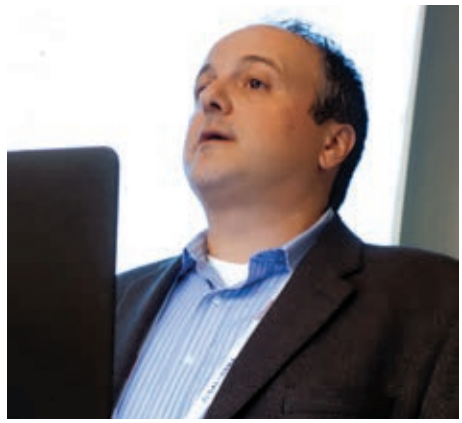
Indeed, the 1% tapinarof cream groups separated from controls in terms of the efficacy endpoints as early as week 1, with the maximum treatment effect seen at weeks 8-12, Dr. Peppers added.

The primary endpoint was a composite requiring both an IGA of 0 or 1, meaning clear or almost clear, at 12 weeks, along with a minimum 2-point improvement on the IGA from baseline to week 12. This was achieved in 46% of patients on tapinarof cream 1% applied once daily, 53% of those on tapinarof cream 1% twice a day, and in about 25% of controls on vehicle.

"THE 1% TAPINAROF ARM SHOWED HIGHER EFFICACY ... THAN THE 0.5% OR VEHICLE."

Eighty percent of subjects who achieved the primary endpoint maintained that level of treatment effect 2 weeks post treatment, and 70% still held their treatment response 4 weeks after they stopped using the medication.

There were two secondary endpoints. One was achievement of a 75% improvement from baseline on EASI scores response. This was seen in 51% of the tapinarof 1% once-daily group, 60% on twice a day therapy, and 26% and 25% of controls. Onset of action was fastest with tapinarof cream 1% once daily.


DR. PEPPERS

The other secondary endpoint was at least a 3-point improvement from baseline to week 4 on the 11-point self-rated itch scale. This was achieved by 37% and 33% of patients on tapinarof cream 1% once daily and twice daily, respectively, a success rate twice that seen in controls.

Four percent of patients on tapinarof cream and 7% on vehicle discontinued the trial because of treatment-emergent adverse events. There were no serious treatment-related adverse events. The most frequent adverse events associated with tapinarof were folliculitis and contact dermatitis. The phase 3 trial will incorporate patch testing for contact dermatitis.

"We are very excited about this program. This will be the first topical therapy – if we're able to achieve treatment success and ultimately regulatory approval – that would be able to treat both psoriasis and atopic dermatitis since topical steroids," Dr. Peppers said.

The study was funded by GlaxoSmithKline and presented by a company employee.

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Parents taking photos of children's lesions for telederm diagnosis looks promising

BY CATHERINE COOPER NELLIST
FROM JAMA DERMATOLOGY


YURI_ARCURS/DIGITALVISION/GETTY IMAGES

Parents generally can take photographs of good enough quality to allow accurate teledermatology diagnoses to be made of many pediatric skin conditions, said Daniel M. O'Connor, MD, of the Children's Hospital of Philadelphia, and his associates.

Skin conditions make up 10%-30% of the approximately 200 million pediatric outpatient visits each year, Dr. O'Connor and his colleagues said. But there are fewer than 300 board-certified U.S. pediatric dermatologists for the nation's nearly 75 million children. So, the possibility of using photos taken by parents for distant pediatric dermatologists to assess is an attractive one.

In a study of 40 patient-parent dyads, parents took photos of their child's lesions with smartphones and sent the images to pediatric dermatologists. The children's lesions were later assessed in person by a pediatric dermatologist.

Concordance between photograph-based vs. in-person diagnosis was 83%. In three cases, diagnoses could not be made by the remote dermatologist because of poor photograph quality. When those cases were excluded, concordance was 89% between photograph-based vs. in-person diagnosis. Concordance for birthmarks was 100%, 92% for rashes, and 64% for alopecia-related diagnoses. Of four cases that were misdiagnosed, there were three cases of alopecia and one nodule.

Half the parents received a simple, three-step instruction sheet on smartphone photography. There was no statistical difference in diagnostic concordance between the parents who received the instruction sheet and those who didn't.

"When dealing with categories with low concordance, such as alopecia and nodules and tumors, teledermatology practitioners may need to be cautious about attempting definitive diagnoses in some cases and may need to refer patients for in-person consultation," Dr. O'Connor and his associates wrote. "For these cases, teledermatology may still serve as a triage tool. For example, patients with suspicious nodules could be referred for expedited appointments in specialty clinics, whereas patients with isolated alopecia could be scheduled for routine visits. Conversely, in diagnostic categories with high concordance, such as birthmarks and rashes, certain cases could be definitively diagnosed and treated exclusively using teledermatology (for example, mild acne)."

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SOURCE: O'Connor DM et al. JAMA Dermatology. 2017 Nov 15. doi: 10.1001/jamadermatol.2017.4280.

COMMENTARY **BY DR. SIDBURY**

CELL PHONE CONSULTS have become a fact of modern medical life. Particularly for parents, this medium is tremendously convenient.

Unfortunately in my experience, it can come at the cost of diagnostic confidence. Dr. Daniel M. O'Connor was able to demonstrate impressive concordance between photograph-based diagnosis and in-person assessment. This involved a simple but specific three-step set of instructions that my "consults" certainly do not; this standardization may be the key. At the very least, when access to specialists is limited, photo triage can be a viable stopgap. As this practice gains traction, standardizing issues around liability and billing may prove as vexing as those of image quality.

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GLOBALACADEMYCME.COM/DERMATOLOGY

Tips for managing dermatologic surgery procedures in children

BY DOUG BRUNK
REPORTING FROM WCPD 2017

CHICAGO – True complications in pediatric dermatologic surgery probably aren't that frequent, but no solid data on the topic exist in the medical literature.

"An appropriate and thorough perioperative evaluation and planning may limit complications," Harper N. Price, MD, said at the World Congress of Pediatric Dermatology.

Dr. Price, chief of the division of pediatric dermatology at Phoenix Children's Hospital, shared general approaches to managing pain, infection, and suture reactions in children who are undergoing dermatologic procedures.

The first step is to make the child comfortable in the office or OR setting; this can include approaching children slowly unless you know them well. "Sit at their level, because coming up very fast and being over ... them is intimidating," she advised. "Make sure you include the child in the conversation you're having; it elicits more trust and belief in what's going to happen. You want to explain what's going to happen in a friendly manner. I think sometimes we have residents who are new to pediatrics that come in and say, 'We're going to cut this out,' and the next thing you know, the child's in tears. Describe what the procedure is going to be like in words that they can understand, and whatever you do, do not lie about what's going to happen."

Dr. Price also makes it a point to cover surgical trays before they're wheeled in. "They don't need to see needles and sharp objects," she said. "Even afterward, bloody gauze can be scary to kids." Positioning the patient properly also is important. "We'll wrap young children up in a swaddle," she said. "In my opinion, you should not be forcefully restraining an older child. They need to cooperate and it needs to be a safe procedure, otherwise, you should consider doing it in the operating room. I never enlist a parent to hold or restrain a child."

One key to managing pain during dermatologic procedures in children comes down to anticipation: What kinds of distractions might the child need? What preoperative analgesia will be required? What postoperative pain medications should be used? "We know that certain procedures in children might be more painful, such as nail procedures, ablative laser procedures, and large excisions with extensive undermining," Dr. Price said. "Pain is subjective and differs from child to child in the way it's experienced, so you need to consider the child's age, coping style, and temperament, and what their history of pain is like. We know that inadequate pain control in children has a negative impact and a negative implication on their future health care interventions, as well as their reactions to further pain."

"SIT AT THEIR LEVEL, BECAUSE COMING UP VERY FAST AND BEING OVER ... THEM IS INTIMIDATING."

Parental involvement can sometimes help. "I like a parent to stay in the room if I'm doing a procedure in the office, as long as they agree to stay seated," she said. "It may make your office staff more anxious, and it may make parents more anxious, too, so it's something to think about." There is some evidence that having a parent present during an in-office procedure increases parental satisfaction as well.

In an effort to minimize pain and anxiety before in-office procedures, Dr. Price and her associates at Phoenix Children's Hospital often use instant ice packs. "They get cold really fast, they're cheap, and you don't have to run to a refrigerator to get ice," she said. Other beneficial measures include topical anesthetics and breathing techniques, such as having the child blow on a pinwheel, blow bubbles, or perform diaphragmatic breathing. Using distractions – stuffed animals, picture books, or video games on a tablet – also can help. "If the child is going to the OR, using preoperative midazolam can help relax the child, especially if they're having repeated procedures," Dr. Price said. Oral sucrose solution in infants, especially in young infants, provides about 5-8 minutes of temporary analgesia and can be placed on their pacifier or their tongue, she added, noting that ethyl chloride spray also can be helpful prior to injections.

During the procedure itself, counter-stimulatory methods can be helpful; this can include handheld devices that use a combination of vibration, ice, and distraction methods. "Buffer your lidocaine and don't inject cold lidocaine; that hurts a lot more," she recommended. "Inject slowly; inject deep. If you have a painful procedure and you're in an OR setting where you give Marcaine [bupivacaine], put that in at the end of the procedure for short-term postoperative pain relief." After the procedure, it's better not to apologize for causing pain or if the procedure didn't go well. "Give positive incentives like stickers and stuffed animals, and use a dressing wrap with

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bright colors," she said. "We often doctor-up stuffed animals in the OR so when [the children] wake up, they have something fun to look at."

Postoperatively, the best way to prevent pain is to recommend limited physical activity. "Children become active quickly after a procedure, and then they hurt," Dr. Price said. "For extremity wounds, consider ice and elevation. I like bulky dressings to prevent trauma, to remind the families that they've had a procedure done. They can usually keep them on for several days."

Surgical site infections are uncommon, but if they do occur, it's usually between postoperative days 4 and 10. "The biggest indicator of an infection in my opinion is pain," she said. "If they're having a lot of pain, I would be concerned. Causes may be the presence of bacteria on the skin or mucosa or improper wound care at home."

The risk factors for surgical site infections in children are not well defined in dermatologic surgery, Dr. Price added, "but we know that if you're going to be operating in the diaper area, that's a place where you're going to have a high risk of infection. Preoperative hair removal – if you shave the scalp before surgery creating small nicks – could [introduce] bacteria. And it's likely that the overall health of the patient may impact their risk of infection. You want to know the difference between normal wound healing and an infection. Culture it. If you're worried, you may want to start empiric antibiotics. If you have a severe infection, something with necrosis, fluctuance, or dehiscence, you might want to consider partially opening that wound and letting it drain and heal in by secondary intention."

POSTOPERATIVELY, THE BEST WAY TO PREVENT PAIN IS TO RECOMMEND LIMITED PHYSICAL ACTIVITY.

Measures to prevent postoperative infections include perioperative counseling to restrict excessive activity to prevent trauma, bleeding, and dehiscence; use of bulky dressings, and explicit wound care instructions. "My nurse calls [the patient's family] the day after a procedure, and I usually have them come in for a wound check, even if there are no sutures to remove, just to make sure things look OK," she said.

Suture reactions are another potential complication of dermatologic surgery in children. The incidence is unknown, but suture reactions usually occur around 6 weeks postoperatively and tend to happen more often in older children. "Excessive reactions, while uncommon, can lead to an increased risk of dehiscence, infection, and delayed healing," Dr. Price said. Small caliber monofilament sutures are less reactive than are large-caliber, multifilament sutures, she added, while synthetic and nonabsorbable sutures are less reactive than natural materials such as silk and surgical gut. Dr. Price favors using poliglecaprone, polyglactin 910, and polypropylene.

Tips for minimizing suture reactions include the following: Use the smallest-caliber suture appropriate for the wound; avoid buried sutures too close to the surface of the skin; use a smaller-caliber suture at the end of excisions, where there tends to be less tension; and keep knots small and flat at the apexes of excision. "Manage suture reactions with reassurance," she said. "The nice thing is that these often heal fine without any delay. When possible, remove the offending suture material. A lot of times, I'll use sterile forceps. At home, I'll have [parents] massage the area with warm compresses to try to extrude the suture. But, if you wait long enough, it usually comes out."

Dr. Price reported having no financial disclosures.

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COMMENTARY **BY DR. EICHENFIELD**

CUTANEOUS PROCEDURES in children include small biopsies, "scoop shaves" of nevi and other skin growths, as well as larger procedures including excisions and laser surgeries of varying size lesions. It is clear that a well-thought-out approach to managing anxiety and pain related to procedures really can improve the experience for children and their families. The "tricks and tips" that can be used vary greatly by the child's age and the procedure being performed. Explaining the procedure in a simple, understandable way is key, and this may be directed to the parents as well as the child. It also is helpful to assess the child's past health care experiences. For example, asking a parent if a 7-year-old has had dental procedures and how she has done with them is very informative, as the answers range from "she did really well" to "we had to put her under general anesthesia for that."

Tips advocated by Dr. Harper N. Price and others include ice packs, topical anesthetic use, distraction techniques including tablet/phone games and videos, pinwheels, bubble blowing, vibration, counterstimulation with pinching, oral sucrose for babies, and parental presence in the room. Pain of injections can be minimized by using buffered lidocaine, warming solutions to body temperature, and slow, deep injections. Rewards are key – I continue to be amazed by the joy that stickers bring! Finally, good postoperative care is quite important to get the best results from pediatric dermatologic procedures, avoiding infections, and poor healing including dehiscence.

Sebum inhibition steps up against acne

BY HEIDI SPLETE
REPORTING FROM SDEF LAS VEGAS DERMATOLOGY SEMINAR

In the future, topical agents that target sebum production could play a greater role in acne management.

Linda F. Stein Gold, MD, director of dermatology research at the Henry Ford Health System in Detroit highlighted several studies of these investigational therapies in a presentation on acne at the Skin Disease Education Foundation's annual Las Vegas Dermatology Seminar.

Sebum reduction has emerged as a focus of acne treatment, she said, with the following trio of candidates in the pipeline:


DR. STEIN GOLD

- SB204, a topical agent that releases nitric oxide.
- DRM01, a topical sebum inhibitor that inhibits acetyl coenzyme-A carboxylase, an enzyme involved in the synthesis of fatty acids.
- Cortexolone 17a-propionate (CB-03-01) 1% cream, a topical antiandrogen.

A 4% gel formulation of SB204 once a day was compared with a vehicle, also applied topically once a day, in a pair of phase 3 randomized, multicenter pivotal trials of 2,639 patients aged 9 years and older with moderate to severe acne, Dr. Stein Gold said. At 12 weeks, the absolute change in number of noninflammatory lesions among those treated with SB204 was a reduction by 15.4 vs. 13.4 among those treated with a vehicle in one study ($P = .03$) and by 14.9 vs. 12.3 with a vehicle in the other study ($P = .001$). The absolute change in the number of inflammatory lesions among those using SB204 in the first study was not significantly different from those seen among patients using the vehicle (a reduction of 12.1 vs. 11.1, respectively) but was significant in the second study (a reduction of 12.9 vs. 10.6 for vehicle; *P* less than .001).

No new safety signals were observed and treatment was "generally safe and well tolerated," with fewer than 2% of patients discontinuing treatment because of treatment-emergent adverse events, she noted.

In a phase 2 study, those treated with a 4% formulation of SB204 had a significant reduction in inflammatory and noninflammatory lesions at 12 weeks, with mild local irritation as the main adverse effect, she said (J. Drugs Dermatol. 2016 Dec 1;15[12]:1496-527). The treatment was generally safe and well tolerated, said Dr. Stein Gold, one of the study authors.

In a phase 2 randomized, multicenter, double-blind study of 108 patients with moderate or severe acne, she continued, those treated with DRM01 7.5% applied to the face twice a day for 12 weeks, those treated with DRM01 showed significant improvement across all efficacy measures at 12 weeks, including a significantly greater reduction in both inflammatory and noninflammatory lesions, and on measures of investigator's global assessment – after 12 weeks of twice-daily treatment. Treatment was well tolerated, and no serious adverse events related to the treatment were reported, Dr. Stein Gold said.

(In October, the manufacturer, Dermira, announced that patient enrollment in two phase 3 trials of DRM01– now known as olumacostat glasaretil – in patients aged 9 years and older with facial acne had been completed.)

Phase 3 studies of cortexolone 17a-propionate (CB-03-01) 1% cream are underway, Dr. Stein Gold said.

SEBUM REDUCTION HAS EMERGED AS A FOCUS OF ACNE TREATMENT, WITH A TRIO OF CANDIDATES IN THE PIPELINE.

Dr. Stein Gold disclosed relationships with multiple companies including Galderma, Leo, Novan, Valeant, Dermira, Novartis, Celgene, Allergan, Foamix, Promius, Anacor, and Medimetriks.

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COMMENTARY **BY DR. EICHENFIELD**

WORKING TO FIND more therapies for acne, there are several clinical trials that involve novel agents with different targets than traditional topical retinoids or antibiotics. Topical agents that release nitric oxide locally or target sebum by inhibiting acetyl coenzyme-A carboxylase, as well as a topical antiandrogen are in clinical trials. Whether these will ultimately make it to the market are unknown; we don't have published papers on the agents highlighted by Dr. Linda F. Stein Gold, and public announcements of trial results of DRM01 and SB204 have not shown clear efficacy data. We look forward to innovations to help us with our acne care.

How you can recognize and treat bug infestations in children

BY JENNA BOROK

Pruritic bug infestations are a common problem among school-age children, Albert C. Yan, MD, said at a pediatric dermatology meeting sponsored by Rady Children's Hospital-San Diego and the University of California, San Diego.

DR. YAN

There are four basic bug infestations – cutaneous larva migrans, carpet beetle dermatitis, scabies, and lice – and it is essential for you to be able to recognize and treat these appropriately. You also need to know resistance patterns, and how to counsel patient on full treatment protocol.

Cutaneous larva migrans typically present with a skin rash on the feet or thighs of children and young adults who walk around barefoot. The organism invades through the skin of the foot and creates serpiginous patterns. *Ancylostoma braziliense* is the most common species to cause this rash. The parasite is usually trapped by the basement membrane and rarely penetrates to visceral organs. However, rarely it can present in the oral mucosa when contaminated products are placed in the mouth, which is why Dr. Yan tells his own kids "not to eat things off the ground." The treatment for this infection includes ivermectin, albendazole, or thiabendazole.

Carpet beetle dermatitis presents in children with a history of spending lots of time on a carpet, presenting with nondescript itchy patches on skin areas that were in contact with the carpet. Carpet beetle dermatitis is becoming more common on the East Coast. Patients actually can find these beetles, which have tiger-striped coloring and have little prickly hairs that stick out of them, in their carpets. The beetles do not bite; rather, the rash is a reaction from exposure to insect blood or the larval hairs. The adult beetles tend to feed on carpet fabrics, wool, grains of food products, animal material, or nectar and pollen in flowers. The treatment is to get rid of the beetles. To rid the house of the beetles, it is rec-

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COMMENTARY **BY DR. SIDBURY**

THE FIRST QUESTION many parents ask after receiving a diagnosis of "bug bites" is "which bug?" This can be an impossible question to answer making a sometimes-fraught discussion (this diagnosis is not always well received) more difficult. The second point parents emphasize when diagnostic doubt arises is the lack of other affected family members; this would seem contrary to a biting pest in the house. My co-conspirator Dr. Eichenfield once taught me to preempt this doubt by leading with the fact that often only one family member is affected. A bite reaction is just that: a bite followed by a hypersensitivity response manifesting as itch and rash. As with any hypersensitivity reaction, some individuals will react and some will not.

Dr. Albert C. Yan helps us further by describing suggestive features of different types of "arthropod assault." Cutaneous larva migrans declares itself by distribution: typically, the foot of a patient who has gone shoeless in an endemic area. Likewise carpet beetle dermatitis presents with itchy red patches at exposed sites; the beetles do not bite but some children react to exposure. Scabies infestation causes a range of cutaneous manifestations both acutely and subacutely. Telltale burrows or linear lesions on the palms and soles, wrist, interdigital web spaces, and even genitalia are more diagnostically helpful (and where any scrapings should be done ideally) than are more nondescript papules.

Pediatricians should remember that symptoms of itch can persist for days to weeks after successful treatment and topical corticosteroids or emollients help most. Further removed from active infection, some children will develop recurrent crops of extremely pruritic papules and pustules, especially on the feet called acropustulosis weeks to months after treated infection; a more nodular hypersensitivity reaction called "postscabetic nodules" also can occur and may take months to years to fully resolve. Awareness of earlier scabies infections can allay what otherwise can appear to be morphologically distinct and concerning lesions.

Head lice remain the least harmful "dreaded" diagnosis of the elementary school parent. Diagnosis is typically straightforward as children, especially girls aged 4-12 years, have new onset scalp itching especially behind the ears and at the occiput. Over-the-counter pyrethrin-based therapies still are first line but resistance is common. Treatment failure may result from inadequate nit combing as this can be a time-consuming and exacting task, especially in children with long hair. Dr. Yan highlights some of the treatment alternatives including topical ivermectin lotion, which has ovicidal properties, but alas, we do not yet have a single-use magic bullet short of head shaving for all cases of head lice.

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ommended to vacuum, remove contaminated food sources, freeze stuffed animals for 10-14 days, and have an exterminator visit the home. Bringing in fresh-cut flowers from the garden without rinsing them may bring the beetles into the house.

Scabies tends to be an itchy, widespread dermatosis. It is associated with extensive small skin papules scattered across the body with linear or curvilinear burrows and tends to present from the elbows or knees distally, especially in webbed areas, such as between the fingers. Keeping these geographic locations in mind makes it easier to differentiate scabies from hand dermatitis and eczema, said Dr. Yan, chief of pediatric dermatology at Children's Hospital of Philadelphia and professor of pediatrics and dermatology at the University of Pennsylvania, Philadelphia.

To help diagnose this infestation, scrape the lesion and visualize the mite, the scybala or mite feces, or the oval eggs under the microscope.

The treatment is a "permethrin party." Luckily, the scabies mite has very little documented resistance to permethrin 5% cream. However, with recurrent treatment, resistance starts to develop, he said. Proper administration is critical in controlling the infestation. For an adult, use 3 ounces or one tube, and for a child, use about 1.5 ounces for a child or one-half a tube. Apply it to the skin from neck down, leave it on for 8 hours overnight. Treat the patient and family members or close contacts. Repeat this application in 1 week. Oral ivermectin is effective and is useful in older kids who may not adhere to the permethrin.

THE TREATMENT IS A "PERMETHRIN PARTY." HOWEVER, WITH RECURRENT TREATMENT, RESISTANCE STARTS TO DEVELOP.

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Pediculus humanus capitis*, the head louse, is an insect of the order Anoplura and is an ectoparasite whose only host is humans.*

A commonly encountered problem is apparent treatment failure. The scabies may be identified, treated, and then they appear to recur. Some patients have persistent postscabetic itch – the patients are still itchy afterward, but the lesions look excoriated and different than the original scabies lesions. The patient does not need retreatment, Dr. Yan emphasized. Rather, use topical corticosteroids or antihistamines to treat the itch.

Another explanation is improper use of medication – for instance, only certain parts of the skin were treated or all family members had not been treated. In this case, everyone needs to be retreated, he said. Reinfection is possible, but resistance is unlikely. Patients with scabies sometimes develop scabetic nodules or hypersensitivity nodules. Often, these are leftover areas of inflammation that can remain for up to 1 year. Dr. Yan recommends treating these areas with low-dose topical steroids.

The last phenomena presents with recurrent crops of pustules in the acral area, which is acropustulosis of infancy or postscabetic pustulosis. This is a variant of acropustulosis of infancy, in that it is more likely to involve the torso than is traditional acropustulosis and tends to be cyclical in that it reappears every few weeks.

Head lice are an "easy" diagnosis, and Dr. Yan describes finding the actual lice on a patient's head as "very satisfying." They are usually found behind ears, on the posterior aspect of the head, and on the neck. Head lice are very common, affecting approximately 6-12 million people per year, and $100 million is spent annually on treating these infestations. It is more common in 3- to 12-year-old girls, usually more prevalent with longer hair, and is spread primarily through direct contact. Live nits are 1-2 mm from scalp, hatch about 1 week later, live for 1 month, then reproduce, while the original nits die off. The lice cannot survive more than 1-2 days off the human body. Infestations tend to be cyclical throughout the year, with an increased number of cases at the end of school year or during the summer.

Recently, the Journal of Medical Entomology published study findings in which head lice genetics were assessed, raising the concern about the development of "super lice." However, this information has not yet brought treatment changes.

The conventional treatments include Nix, Rid, Triple X, but there can be a fair amount of resistance with these OTC treatment. Other options include mayonnaise and olive oil, however, not much data support the efficacy of this treatment. There are three prescription medications available: benzyl alcohol lotion, spinosad topical suspension, and ivermectin lotion. Start with these treatments quickly when dealing with lice that are resistant. Oral ivermectin also is effective. Dr. Yan concluded his lecture with discussion of other techniques that have been cleared by the Food and Drug Administration, such as blow-drying the lice off the head, if one is okay with them landing in the office!

Dr. Yan reported no relevant financial disclosures.

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Children with psoriasis face multitude of potential problems and comorbidities

BY DOUG BRUNK
REPORTING FROM WCPD 2017

CHICAGO – Children with psoriasis face a multitude of potential problems and comorbidities, ranging from anxiety and depression to obesity and metabolic disease, so early and proactive identification is key.

"These children are more likely to engage in high-risk behavior such as use of alcohol, tobacco, and drugs – a trend that continues into adult ages," Kelly M. Cordoro, MD, said at the World Congress for Pediatric Dermatology. "They also have a higher association with inflammatory bowel disease, among other conditions. Those of us who care for pediatric psoriasis patients are on the front lines of recognition of these potential comorbidities, which allow for, ideally, prevention and certainly, early intervention."

Arthritis is one of the first understood comorbidities of psoriasis in adults and children, said Dr. Cordoro, a pediatric dermatologist at the University of California, San Francisco, Medical Center. In children with the condition, arthritis commonly affects the hands and feet, but it can also affect larger joints such as the hips, the knees, and the back. "The prevalence range is very broad, probably between 10% and 40%," she said. "Severe nail and distal digital psoriasis is predictive of arthritis, so we need to be thinking of that and not forgetting that children can get arthritis."

Obesity ranks as the most well understood comorbidity of psoriasis in children. Study after study has demonstrated this association. In addition, obese children with psoriasis also may harbor components of the metabolic syndrome – hypertension, dyslipidemia, and diabetes. "They're not as much at risk for metabolic syndrome in the absence of obesity, but there's still a small signal," Dr. Cordoro said. "We ask ourselves this question as clinicians: Are these pediatric patients at risk for cardiovascular and cerebrovascular disease as they get older? In other words, what is the health of a 6-year-old, obese child with severe psoriasis, who may also have other components of the metabolic syndrome, going to be like when he is 35 or 40? Are these the children who go on to have cardiovascular events as documented in adult studies of psoriasis?"

To date, several studies have identified a clear link between psoriasis and obesity, and between psoriasis and hypertension, diabetes, and dyslipidemia in certain populations. "There is a dose-response effect," Dr. Cordoro said. "The more severe the psoriasis, the more likely the patient is to be obese, and vice versa." In one study, researchers analyzed 409 psoriasis patients up to age 17 years in nine countries (JAMA Dermatol. 2013;149:166-76). They concluded that globally, children with psoriasis have excess adiposity and increased central adiposity regardless of psoriasis severity. The researchers used multiple measures of adiposity, not just body mass index (BMI), but also waist circumference and waist-to-height ratio. "Waist circumference and waist-to-height ratio are surrogates for central and visceral adiposity," said Dr. Cordoro, who was involved with the study. "And central adiposity may be a more sensitive indicator of metabolic disease and cardiovascular risk than BMI alone."

Another study demonstrated that high adiposity preceded psoriasis by up to 2 years in 93% of overweight or obese psoriatic children (JAMA Dermatol. 2014;150:573-4).

In a more recent analysis, researchers evaluated lipid function in 44 psoriatic children (J Invest Dermatol. 2016;136[1]:67-73). Compared with age-matched controls, children with psoriasis were found to have higher waist-to-hip ratio, higher insulin resistance, and 27% were obese. "There was no difference in fasting lipid levels but the blood profiles had atherogenic markers that are worrisome for ongoing risk for atherosclerosis, cardiovascular disease, and

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COMMENTARY **BY DR. EICHENFIELD**

IT IS AN EXCITING yet challenging time for the field of pediatric psoriasis! The impact of the disease is better understood, as studies show the potential comorbidities associated with having psoriasis may impact the health of affected individuals throughout their lifetime. The article covering Dr. Kelly M. Cordoro's discussion at World Congress of Pediatric Dermatology highlights the associations that should be considered in any child or adolescent with psoriasis: obesity, metabolic disease, arthritis, dyslipidemia, anxiety, and depression. There is clear evidence of adults with psoriasis having higher risks of atherosclerosis, and cardiovascular and cerebrovascular disease, and that the inflammation of psoriasis has systemic and not just cutaneous effects.

Increased risks of autoimmune diseases, including rheumatoid arthritis, vitiligo, inflammatory bowel disease, and thyroiditis also should be kept in mind, based upon work utilizing the Danish national health information registries presented by Christoffer Blegvad, MD, in a recent congress of the European Academy of Dermatology and Venereology.

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Adalimumab outperforms methotrexate in treating severe pediatric plaque psoriasis

BY CATHERINE COOPER NELLIST
FROM THE LANCET

Adalimumab appears to be a safe and effective treatment option for severe plaque psoriasis in children, outperforming methotrexate, based on the results of a phase III study, said Kim Papp, MD, PhD, of Probity Medical Research, Waterloo, Ont., and his associates.

"To our knowledge, this is the first randomized controlled study of either adalimumab or methotrexate in children and adolescents with psoriasis," the researchers said, noting that the study did not include a placebo group because of ethical issues related to treating children with a severe chronic disorder.

The double-blind, phase 3 trial was done at 38 clinics in 13 countries with 114 children aged 4-17 years with severe plaque psoriasis who had not responded to topical therapy. They were randomized to receive 0.8 mg/kg (up to 40-mg total dose) adalimumab (38 patients), 0.4 mg/kg (up to 20-mg total dose) subcutaneously at week 0 and

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cerebrovascular disease," she said.

Research among adults has demonstrated that psoriasis confers an independent risk of atherosclerosis, MI, stroke, and early cardiovascular-related mortality, the so-called "psoriatic march." Theoretically, Dr. Cordoro said, severe psoriasis sets up a state of chronic systemic inflammation, which leads to insulin resistance, which predisposes affected individuals to endothelial dysfunction, and eventually can lead to atherosclerosis. "When atherosclerosis becomes unstable, now you've gone from having severe psoriasis into a situation where the chronic inflammation may have predisposed you to having a thrombotic event such as a heart attack or stroke," she said. "Obesity replicates that same pattern. What does this all mean? Is this real or is this just a theory? We don't know, but it's certainly biologically plausible. It's not been proven with long-term prospective studies, which we need."

Dr. Cordoro went on to discuss the importance of assessing young psoriasis patients for psychiatric and emotional comorbidities, including anxiety, depression, and eating disorders. "These kids can become socially isolated, which can lead to more downstream effects: more anxiety, more depression, sometimes overeating and obesity," she said. "It's not only that the patient has situational anxiety or depression, the notion that 'My skin looks terrible. I'm really depressed about it;' it's more than that. It turns out that the same inflammatory milieu in psoriasis lesions can be replicated in the brain inflammatory milieu in patients with depression and other psychiatric disorders. That's fascinating to recognize that these comorbidities can be intrinsic. There's a biological basis and not just a downstream effect."


DR. CORDORO

She advises clinicians who care for children with psoriasis to keep potential comorbidities in mind, and to make sure families understand that there can be psychiatric, emotional, and physical consequences to undertreated disease. "We do not yet know how to risk stratify these patients. At the very least, you want to identify overweight or obese children with moderate to severe disease for early intervention," Dr. Cordoro said. "Weight loss and lifestyle interventions are the hardest goals to accomplish but are really critical. Prevention is the best strategy. We can help ourselves and help our patients by referring to obesity and nutrition experts who can not only help the child but get the entire family involved."

In a consensus statement published online in JAMA Dermatology, a multidisciplinary panel of experts including Dr. Cordoro offer an evidence- and consensus-based approach to screening children with psoriasis, based on a review of 153 manuscripts in the medical literature. The panel recommends that all psoriasis patients 2-21 years of age should undergo annual measurements of blood pressure and BMI, and screenings for arthritis and mood disorders. "These don't have to be formal mood disorder screens," Dr. Cordoro said. "They can be informal questioning about anxiety and depression, like 'How is your psoriasis impacting you? How do you feel about your psoriasis? What do you say when people ask you about your psoriasis?' It's also important to ask overweight patients what they're doing to keep their weight in check. Oftentimes, when you ask a question about mood or impact of disease or stigma or bullying, the child will be completely silent and either stay silent or start crying or start telling you their stories. It's really important to ask, because it validates that their concerns are more than just about vanity but about their overall health, and that is a critical difference."

Dr. Cordoro disclosed that she is a consultant for Pfizer and Valeant.

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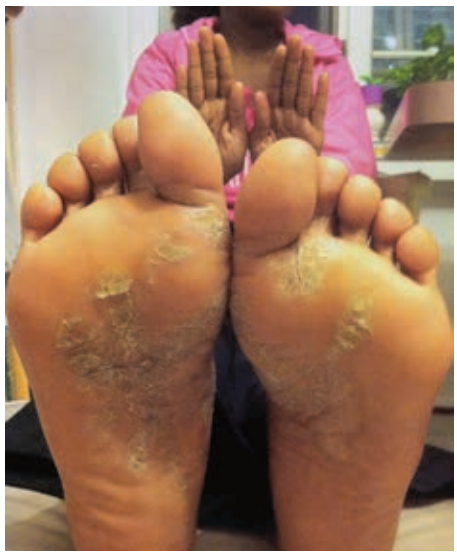
then every other week (39 patients), or 0.1-0.4 mg/kg once weekly of oral methotrexate (up to 25 mg per week total dose; 37 patients). There were four periods to the study: a 16-week period, followed by an up to 36-week withdrawal; a 16-week retreatment period; and a 52-week long-term follow-up. The first three periods were reported in this study.



LORI FARMER/MDEDGE NEWS

At week 16 of the initial treatment period, an improvement of at least 75% in the Psoriasis Area and Severity Index (PASI 75) score was reached by significantly more of the patients in the 0.8 mg/kg adalimumab group – 22 (58%) – than in the methotrexate group – 12 (32%). In the 0.4-mg/kg adalimumab group, 17 (44%) of patients reached a PASI 75. The PASI 75 response was rapid in the 0.8 mg/kg adalimumab group, a significant difference, compared with the methotrexate group. It was reached by week 4 ($P = .002$).

"At week 16, the 26% difference between adalimumab 0.8 mg/kg and methotrexate in the proportion of patients who achieved PASI 75 was significant and clinically relevant," Dr. Papp and his associates concluded.

At week 16 of treatment, the proportion of patients who achieved a physician global assessment score of 0 or 1 (clear or minimal) was higher in the adalimumab 0.8 mg/kg group (23 of 38; 61%) than in the methotrexate group (15 of 37; 41%) or in the adalimumab 0.4-mg/kg group (16 of 39; 41%; $P = .083$). At week 16, the difference between the adalimumab 0.8-mg/kg and methotrexate groups was not significant, the investigators said.

After the withdrawal period, PASI 75 was achieved in 15 of 19 (79%) patients who were initial responders to adalimumab 0.8 mg/kg and 6 of 11 (55%) patients who were initial responders to adalimumab 0.4 mg/kg. PASI 75 was achieved in six of eight (75%) patients who had responded to methotrexate treatment in the initial treatment period and who had loss of disease control in the withdrawal period.

During the initial treatment period, adverse events were reported by 26 of 38 (68%) in the adalimumab 0.8-mg/kg group, 30 of 39 (77%) in the adalimumab 0.4-mg/kg group, and 28 of 37 (76%) in the methotrexate group. Infections were the most frequently reported adverse events. Serious adverse events were infrequent, reported by three patients in the adalimumab 0.4-mg/kg group, and were not considered to be related to the study drug, the researchers said. Eleven severe adverse events were reported by 8 of the 114 (7%) children. Of these, headache was the most common. A case of urticaria during retreatment that led to discontinuation of adalimumab in the patient (who had received methotrexate in the first treatment period), was considered by the investigator as "probably related" to adalimumab.

"No new safety risks were identified in our study; however, longer-term data are needed to fully assess the safety profile of adalimumab in the pediatric population," Dr. Papp and his associates commented.

"Our results showed better quality of life outcomes in children and adolescents treated with adalimumab compared with methotrexate. The mean 10.8-point change in PedsQL [pediatric quality of life inventory] from baseline to week 16 in the adalimumab 0.8-mg/kg group exceeded the minimal clinically important difference of 4.36, whereas the 1.9-point change in the methotrexate group did not," they noted.

The study was funded by AbbVie, the manufacturer of adalimumab (Humira). Dr. Papp has served as a consultant for AbbVie and a number of other pharmaceutical companies, for which he has served as consultant or speaker or on advisory boards. His associates listed numerous similar disclosures. Two authors were AbbVie employees.

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COMMENTARY **BY DR. EICHENFIELD**

PEDIATRIC PSORIASIS has fallen behind to a degree, as the delayed approval of systemic therapy and biologic agents in the United States meant that it was hard to access the therapies that have transformed treatment of adult psoriasis over the past 10 years. However, we now have two biologic agents approved for pediatric psoriasis, etanercept and ustekinumab, and multiple ongoing trials for other medications.

There are more data available on the use of methotrexate for pediatric psoriasis attributable to a collaboration of the Pediatric Dermatology Research Alliance and the European Working Group on Pediatric Psoriasis, and recent studies have compared methotrexate with certain biologic agents, allowing us to compare a long-used medication not approved for psoriasis (methotrexate) with newer biologics.

Supportive care alone linked to worse outcomes in mucocutaneous reactions

BY DOUG BRUNK
REPORTING FROM WCPD 2017

CHICAGO – Pediatric patients with Stevens-Johnson syndrome and toxic epidermal necrolysis who received purely supportive care and surgical debridement had poorer outcomes, compared with other treatment modalities, a systematic review suggested.


MR. MANSOUR

Although rare in the pediatric population – with an incidence of approximately 1 case in 2 million – Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both life-threatening mucocutaneous reactions.

"Several treatment modalities have been proposed among both children and adult populations with variable results. Because of the lack of controlled studies, evaluating those modalities objectively becomes difficult – especially in children," Danny Mansour said in an interview following the World Congress of Pediatric Dermatology.

Because reliable and validated data in the management of these conditions are lacking, he and his associates performed a systematic review to evaluate the effectiveness of reported treatment modalities using specific outcome measures.

"This study is unique in that it aims to not only capture more commonly employed interventions such as supportive care, surgical debridement, intravenous immunoglobulin [IVIG], and corticosteroids but also newer modalities that coincide with our improved understanding of the pathogenesis of the disease, such as the use of cyclosporine and biologics," said Mr. Mansour, a third-year medical student at the University of Toronto.

The researchers systematically reviewed English and non-English articles using a variety of databases. They excluded nonpediatric cases and those in which specific treatment modalities and outcome measures of interest were missing. In all, 302 articles were included in the study – 197 that examined mortality and 105 that examined time for arrest of progression of blistering, re-epithelialization, and length of hospital stay.

The main treatment modalities included supportive care alone, IVIG, corticosteroids, cyclosporine, surgical debridement, and biologics. The average time for arrest of progression of blistering was 8.4 days for supportive care, 4 days for IVIG, 6 days for corticosteroids, 2.5 days for cyclosporine, and 1 for infliximab. No data were available for time to arrest of progression for surgical debridement alone.

The average time for re-epithelialization was 24 days for supportive care, 18 days for surgical debridement, 8.7 days for IVIG, 12.2 days for corticosteroids, 10.6 days for cyclosporine, and 13 days for infliximab. Average length of hospital stay varied from 15.6 days for supportive care, 24.3 days for surgical debridement, 17.4 days for IVIG, 11.5 for corticosteroids, 15.5 for cyclosporine, and 26.3 for biologics.

The overall mortality was 4.6% among those who received supportive care alone, 8.3% among those who received IVIG, 4.5% among those who received corticosteroids, and 0.9% among those who received IVIG plus corticosteroids. Specifically, the rates of mortality for SJS and TEN cases treated with supportive care alone were 2% for SJS cases and 15.3% for TEN cases, respectively. The rates for other treatment modalities were 3.1% and 11% for IVIG, 1.7% and 9.3% for corticosteroids, and 0% and 2.1% for IVIG plus corticosteroids.

"While it was not surprising that mortality rates in pediatric SJS and TEN are low, the rates were slightly higher than anticipated," Mr. Mansour said. "In addition, our data show that, although mortality is not influenced by certain therapeutic interventions in SJS patients, it may play a role in the management of the more severe disease, TEN."

Mr. Mansour had no financial disclosures.

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COMMENTARY
BY DR. EICHENFIELD

SJS AND TEN remain scary conditions, causing tremendous morbidity and occasional mortality in children and adolescents, and average length of hospital stays of 2-3 weeks. There is still great variation in approaches to therapy: IVIG, corticosteroids, cyclosporine, biologic agents such as etanercept, supportive care, and debridement.

The systematic review discussed by Danny Mansour at the World Congress of Pediatric Dermatology found that supportive care alone did not seem to do as well as systemic therapy. However, as pointed out, the study is really limited by its retrospective nature and that the fact that much of the data is from small cohort studies and case reports. We still struggle to know what the best interventions are beyond excellent skin care and supportive therapy, and whether associated etiologies (such as specific drugs or infections) should influence selection of therapies.

Clues to drug adulteration may lie skin deep

BY KARI OAKES
EXPERT ANALYSIS FROM WCPD 2017

CHICAGO – Sometimes, the skin can provide the first clues that a patient has been exposed to a drug product that has been adulterated or an over-the-counter product illegally sold in this country that contains a prescription medication, according to pediatric dermatologist Scott Norton, MD.

Speaking at the World Congress of Pediatric Dermatology, he reviewed some of the reactions associated with exposure to counterfeit drugs, contraband drugs, as well as products, misrepresented as drugs that do not include any active pharmaceutical ingredients. The worldwide market for these products is a "hugely profitable industry," and the scope of the problem should not be underestimated, said Dr. Norton, chief of dermatology at Children's National Health System, Washington.

Examples include completely fraudulent formulations, from fake vaccines being distributed in China and Nigeria and counterfeit antimalarials in Cambodia to "contraceptive" pills in Brazil that contain no contraceptive ingredients. In addition, many Asian so-called herbal remedies are actually adulterated with corticosteroids, antibiotics, and other prescription medications. Another issue, he noted, is that substandard medications might contain too much or too little of the active ingredient listed on the label, including adulterated vehicles or fillers.

Today, patients and their family members who travel out of the country – and even local shopkeepers – may bring in these sorts of products from outside the United States, many of which would require a prescription in the United States.


DR. NORTON

In the United States, there have been several reports of a mysterious fixed-drug eruption in patients reported to have taken Baczol, a cold and flu remedy available over the counter in El Salvador for upper respiratory infections. Two of the ingredients listed on the Baczol label are sulfamethoxazole and trimethoprim, two prescription antibiotics. After determining that two Salvadoran American children with a suspected fixed-drug eruption had taken a Baczol product, Dr. Norton, with the aid of medical students, was able to find Baczol containing trimethoprim-sulfamethoxazole for sale over the counter in more than one-third of the shops visited in the greater Washington area (MMWR 2013 Nov 22;62[46]:914-6). Eventually, the Food and Drug Administration issued a consumer alert regarding certain Baczol products containing these ingredients, but Dr. Norton said he is still concerned about the possibility for more grave hypersensitivity reactions to these sulfa antibiotics in the Salvadoran product.

In the United States, children treated with adulterated preparations for atopic dermatitis may present with striae and other dermatologic stigmata of potent topical steroid use in areas of atopy; for example, one such preparation was found to contain clobetasol. In a commentary recently published online in JAMA Dermatology, Hongfu Xie, MD, and two other Chinese dermatologists described the pervasive presence of topical steroids in Chinese cosmetic preparations (JAMA Dermatol. 2017 Jul 5. doi: 10.1001/jamadermatol.2017.1615).

Sometimes, said Dr. Norton, the problem lies in the lack of an expected ingredient. He and his team at Children's National Health System helped solve a medical mystery involving a skin ailment in very premature infants with cholestasis. An interdisciplinary team was convened after the neonatal intensive care unit at the hospital saw its third infant with severe blistering and erosions in an acral, perianal, and perioral pattern that did not respond to empiric treatment for herpes simplex virus and staphylococcal infection – a pattern reminiscent of zinc deficiency dermatitis. Dietitians reported that there was a nationwide shortage of sterile injectable zinc, so total parenteral nutrition was being formulated without zinc. All three of the premature infants were receiving total parenteral nutrition and were so premature that they had insufficient zinc stores. The problem was identified and corrected (MMWR 2014 Jan. 17;63[02];35-7).

Keeping a lid on counterfeit drugs is challenging, since there are so many potential entry points into the supply chain, Dr. Norton pointed out.

There is some international cooperation to detect and combat drug counterfeiting and adulteration. In the meantime, he emphasized that physicians must maintain a high index of suspicion and keep in mind that the first signs of adulterated drugs or prescription drugs available OTC may appear on the skin.

Dr. Norton reported no conflicts of interest.

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COMMENTARY
BY DR. EICHENFIELD

NOT FAKE NEWS – Fake and fraudulent drugs may be affecting our patients. Dr. Scott Norton discussed fake vaccines, inactive antimalarials and contraceptive pills, and "herbal remedies" with corticosteroids. He stressed that we should maintain a high index of suspicion and query both prescription and over-the-counter products being used when there are unusual findings or unexpected outcomes.

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