



A SUPPLEMENT TO
Pediatric News

PEDIATRIC DERMATOLOGY

**Novel topicals shine
in treating eczema**

**Treatment tips
for molluscum
contagiosum
and warts**

**What role does
diet play in acne?**

**Distinguishing
psoriasis from
atopic dermatitis**

And more . . .

**Commentaries by
Dr. Lawrence F. Eichenfield
and Dr. Andrew Krakowski**

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Reference: I. Weber TM, Samarin F, Babcock MJ, Filbry A, Rippke F. Steroid-free over-the-counter eczema skin care formulations reduce risk of flare, prolong time to flare, and reduce eczema symptoms in pediatric subjects with atopic dermatitis. *J Drugs Dermatol.* 2015;14(5):478-485.

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Skin Science That Shows

Reflections on exciting new findings in the pediatric dermatology field

BY LAWRENCE F. EICHENFIELD, MD

Atopic dermatitis (AD) is the most common inflammatory skin disease in the first few years of life, manifested by eczematous rashes, pruritus, xerotic skin, and a set of atopic and nonatopic comorbidities. There has been significant evolution in knowledge of the pathogenesis of atopic dermatitis. It is now recognized that intrinsic, genetically mediated skin barrier dysfunction, as elucidated with filaggrin gene mutations, explains tendencies to xerotic skin in early life, manifested by increased transepidermal water loss, lower hydration levels, and a “leakier” epidermis that may increase cutaneous sensitization. Filaggrin mutations have been associated with a higher risk of AD development, as well as the development of asthma and food allergy (specifically peanut allergy). Utilization of newer research techniques has helped to “dissect” the inflammatory responses in atopic dermatitis. Th2-driven inflammation has been shown important in the “life of eczema” in the skin. Th2 responses are associated with the production of cytokines that contribute to eczema rashes, mediate itch, and negatively affect the epidermis. Work continues to understand what stimulates the Th2 responses in early life, as well as what specific therapies may be used to dampen inflammation in established dermatitis.

We are on the border of a tremendous breakthrough in therapies for AD. Newer nonsteroid topical agents are well along in clinical trials, showing anti-inflammatory effects without atrophy or impact on the adrenal axis, as they are not corticosteroids. One target for therapy is phosphodiesterase-4 (PDE-4). PDE-4 is upregulated in inflammatory cells in atopic dermatitis, an observation made by Dr. Jon Hanifin (a master of atopic

dermatitis and one of the names behind the standard diagnostic Hanifin-Rajka criteria). Topical PDE-4 inhibitors may be very useful for the management of AD, with the boron-based product crisaborole having completed phase III trials and another product having completed phase II studies.

Systemic therapies for more severe atopic eczema have not been utilized as readily as they probably could be, because of limited studies to support their use and concerns with side effects and toxicities. Cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil have been utilized, but there is a paucity of medical literature in children and adolescents, and few comparative studies of effectiveness and safety. The potential breakthroughs with new biologic and small molecules targeting more specific pathways of AD inflammation are tremendously exciting! Phase III studies are underway in adults of an anti-interleukin-4 (IL-4) receptor antibody (dupilumab) that inhibits IL-4 and IL-13 receptors and has shown excellent promise in phase II studies. Oral PDE inhibitors, approved for adults in psoriasis, may have utility in AD. Other biologic agents are in development as well. Thanks to successful advocacy work organized by the Pediatric Dermatology Research Alliance (PeDRA) and other groups, children and adolescents with severe AD are being included in the clinical studies of these new potentially breakthrough products.

Meanwhile, it is time to change our messages to patients and families: Atopic dermatitis can be effectively managed, and we should work to

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DR. EICHENFIELD

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have each patient with no to minimal rash, itch, or sleep disturbance! Delivering this message will take work, communication, education, handouts, Web and video material, and time. But we should take advantage of the opportunity as we soon will have new tools to help us achieve these goals.

Dr. Eichenfield is chief of pediatric and adolescent dermatology at Rady Children's Hospital–San Diego; professor of medicine and pediatrics at University of California, San Diego; and director of the Rady Children's Hospital/UCSD's Eczema and Inflammatory Skin Disease Center. He has long-standing research interests in atopic dermatitis, acne, and psoriasis, as well as neonatal dermatology and pediatric lasers. Dr. Eichenfield has authored over 300 publications, is co-editor-in-chief of Pediatric Dermatology, is a founder and cochair of the Pediatric Dermatology Research Alliance, and recently served as cochair of the American Academy of Dermatology Task Force on Guidelines of Care for Atopic Dermatitis. Dr. Eichenfield has served as an investigator and/or consultant for Anacor Pharmaceuticals, Otsuka Pharmaceuticals, and Regeneron Pharmaceuticals.

BY ANDREW KRAKOWSKI, MD

The current science surrounding acne management places new importance on the pathogenesis of the condition and the idea that inflammation is present even before it may be clinically apparent (i.e., the “microcomedone”). While acne science continues to evolve, the art of successful treatment remains a separate challenge. True acneologists know that in addition to pathogenesis and defined treatment algorithms, we must consider other factors that, ultimately, affect treatment success.

A primary goal of acne management is clinical resolution of the condition itself. Perhaps equally important should be the ability to prevent permanent scarring, the avoidance of side effects, and the successful psychosocial reintegration of the acne patient into society. From a public health perspective, measures to reduce bacterial resistance and overall health care costs also must be considered.

The articles included herein for commentary raise interesting points to ponder:

- What role does diet specifically play in acne? If we consider food a drug, then should we be surprised that it may have a direct impact on acne? Should we not

be prepared to discuss with our patients the potential interactions of dietary supplements (for example, whey protein) with the conventional acne medications we use?

- Should medications that address the pathogenesis of acne from a multifactorial perspective and that facilitate adherence to a regimen – but may come with a higher price tag – be given first-line status within the acne armamentarium? What realistic role do such combination therapies play when generic topical tretinoin is now being denied as “cosmetic” by some insurance plans?
- How do we balance the public health focus on antibiotic stewardship with an insurance company's requirement that two oral antibiotics be trialed prior to giving authorization for a patient to use isotretinoin? How do you explain such an artificial demand to a teenager suffering from scarring, cystic acne in the present?

As we ask these questions (and then face ourselves in the mirror trying to answer them), it becomes clear that the management of acne is not as straightforward as it may, at first, seem. Clearly, gaps remain in terms of education, treatment approach, patient/payer expectations, and, of course, acceptable clinical outcomes. How did we become so desensitized as to accept acne vulgaris – a near-universal inflammatory medical condition that inflicts untoward psychosocial distress and, quite literally, brands our children's faces with permanent reminders of treatment opportunities missed – as simply a “normal” part of adolescence?

We must evolve our thinking as we continue to advance our knowledge of this inflammatory skin condition and the sequelae and comorbidities that accompany it. Yes, we have a long way to go, and the good news is that articles such as these are helping us get there!

Dr. Krakowski is a board-certified dermatologist and pediatric dermatologist with a clinical research focus on acne, eczema, and the application of lasers/photomedicine in children. He currently serves as the chief medical officer for DermOne, LLC, in West Conshohocken, Pa. He has authored more than 60 peer-reviewed publications, including pediatric-specific acne treatment guidelines endorsed by the American Academy of Pediatrics in 2013. Dr. Krakowski is a regularly invited lecturer and course director for the American Academy of Dermatology, the American Academy of Pediatrics, and the American Society for Laser Medicine and Surgery. He is the pediatric dermatology editor for Practical Dermatology, and the peer-reviewed Journal of Clinical and Aesthetic Dermatology. In 2013, he received LaRoche-Posay's inaugural “Dermatology From the Heart” award for his work with pediatric and adult scar patients. Dr. Krakowski said he had no relevant financial disclosures.



DR. KRAKOWSKI

Expert critiques isotretinoin controversies

BY AMY KARON

AT WCD 2015

VANCOUVER – Controversies surrounding isotretinoin are mostly unfounded, Dr. Neil Shear said at the World Congress of Dermatology.

“Isotretinoin is the most effective treatment for all grades of acne vulgaris,” said Dr. Shear, professor and chief of dermatology at the University of Toronto. “Isotretinoin causes fetal malformations, and most preventative strategies around pregnancy have not been completely successful. Isotretinoin does not cause inflammatory disease, nor irritable bowel, but it can, rarely, cause depression,” he said. “If you agree with all those things, I don’t find it very controversial.”

There’s “a very good argument” for using isotretinoin as a first-line therapy for some patients with acne, said Dr. Shear. “We know the issues behind systemic antibiotics might be larger than the issues behind isotretinoin.”

Safety concerns have spurred dozens of lawsuits, but despite split verdicts and millions of dollars awarded to plaintiffs, the best available evidence does not support a causal association between isotretinoin and inflammatory bowel syndrome, Dr. Shear asserted. He pointed to a large population-based cohort study that found no association between isotretinoin and IBD in its primary analysis, although prespecified secondary analyses linked IBD with both isotretinoin and topical acne medications. “The conclusion could only be that if there is increased IBD, it is associated with acne, not with the therapy,” Dr. Shear said. “The arrow has been pointing us in this direction for over a decade now, and I am hoping there will be bigger studies to show the blame is with acne, not isotretinoin.”

Isotretinoin has been linked with clinical depression, which is sometimes preceded by onset of new headache, Dr. Shear said. “But untreated acne is associated with depression and even suicidal ideation sometimes. I think it’s quite manageable,” he said. “It’s all part of the risk management of

using a medication like isotretinoin. Patients who are depressed with acne, even when they have dry lips and other side effects, are so much happier with isotretinoin.”

Dr. Shear would not rule out isotretinoin for acne patients who have a history of clinical depression, but he would first consider other options such as decreasing dietary glycemic load or retrying “failed” treatments to ensure that patients gave them an adequate trial, he said.

Because of its high risk of severe fetal malformations, dermatologists who prescribe isotretinoin need to ensure that female patients have a specific plan for using effective birth control, Dr.

Shear said. But the risk of birth defects does not negate the need for the drug, he said. “Companies have tried hard to make a similar retinoid that does not affect the fetus and cause birth defects and have not been successful.”

The hypothesis that isotretinoin adversely affects pediatric bone growth has been debunked, Dr. Shear said, in response to a question from the audience, citing a study published in the journal *Osteoporosis International*.

Dr. Shear disclosed ties with Roche, which formerly manufactured and marketed isotretinoin (Accutane) in the United States.

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Commentary by Dr. Krakowski

SEVERAL VERY GOOD STUDIES have helped shed some much needed light on the implication that isotretinoin might cause inflammatory bowel disease. The data simply do not support a direct “cause and effect” relationship. In fact, a few of the studies – depending on your interpretation of the data – hint at a possible protective effect. That finding would make sense if “acne” itself or “inflammation” in general turns out to be the underlying link (if one truly exists) to inflammatory bowel disease, rather than isotretinoin.

As for a link to depression, I have to say that most of my adolescents who successfully complete a course of isotretinoin treatment tend to experience an improvement in overall mood and self-esteem. I have always attributed that to the simple fact that severe acne may shake someone’s confidence or cause a person to question their own self-worth – especially impressionable teenagers still trying to find their place in today’s society. If you make the acne better, you remove at least one of the obstacles in the way of patients feeling good about themselves.

That said, I have absolutely seen

patients get “moody” at higher doses of isotretinoin. You can tell right away because the parent gives you a look like, “What happened this month to our nice teenager?” You hear that your patient is fighting more with the parents or siblings or appears to be less engaged in activities he or she had previously enjoyed. What is hard to piece out is whether this is an isotretinoin effect or simply a sullen teenager effect. Either way, I take it seriously and, in these cases, back off on my dosing and demand close follow-up.

Typically, I do not deny isotretinoin to an adolescent with a documented or suspected history of depression. Instead, I ask that the patient and family partner with me to coordinate care with a psychologist or psychiatrist. Prior to initiating isotretinoin, the patient gets a baseline assessment of psychological status, and the mental health provider must agree to see the patient on a monthly basis, through the entire course of treatment. I keep a close eye on these patients and titrate the dose of isotretinoin based on feedback I get from the mental health provider and the patient and family.

New options for acne treatment

BY KARI OAKES

EXPERT ANALYSIS FROM SDEF LAS
VEGAS DERMATOLOGY SEMINAR

LAS VEGAS – New acne treatment strategies that address the issue of antibiotic resistance include subantimicrobial dosing; new, narrower-spectrum antibiotics; and topical use of tetracycline-family antibiotics, according to Dr. Linda Stein Gold, a dermatologist at Henry Ford Hospital, Detroit.

Oral antibiotics have long been a mainstay of acne treatment, but long-term use of low-dose antibiotics may be contributing to the global crisis of antibiotic resistance. At least 2 million people become infected with resistant bacteria yearly in the United States alone, and at least 23,000 people die yearly from these infections, she noted.

“In dermatology we use antibiotics quite a bit, and we want to make sure when we’re utilizing drugs, we’re utilizing them in the best possible way,” Dr. Stein Gold said at the Skin Disease Education Foundation’s annual Las Vegas dermatology seminar. Finding the right antibiotic dose for effective treatment of acne can be a challenge, she noted. “Is more better? Is too little bad?”

In a review of new treatment strategies that address these concerns

without compromising efficacy, Dr. Stein Gold said that the rationale for using subantimicrobial antibiotic dosing comes from the anti-inflammatory effect seen with many antibiotics, even with doses lower than needed for antimicrobial action.

For example, a study of a subantimicrobial-dose of doxycycline found that when adults with moderate acne were treated with the antibiotic (20 mg, twice daily) for 6 months, their acne significantly improved. The number of comedones, inflammatory lesions, and noninflammatory lesions improved significantly compared with those on placebo (*Arch Dermatol.* 2003 Apr; 139:459-64).

In another head-to-head trial that compared low-dose modified-release doxycycline with placebo or 100 mg of doxycycline, the lower dose outperformed both placebo and full-strength antibiotics. No resistant organisms were found among skin flora in the subjects, and the microbiota of the patients’ skin did not change significantly during the study period, she said.

Dr. Stein Gold’s work also suggests that systemic antibiotics may not be necessary for all patients with acne: In a study, after 12 weeks of treatment, adapalene plus benzoyl peroxide, in combination with doxycycline, re-

sulted in significantly more patients with clear or almost-clear skin than with vehicle alone plus doxycycline. “Antibiotics are not always the golden nugget in the treatment of acne,” she commented.

Another tactic is to treat with antibiotics for a period of 3-6 months along with potent topicals, to get skin clear or almost clear, then discontinue the antibiotic and continue topical treatment. Many patients will be able to maintain clear skin on this regime, she noted.

A new tetracycline-family antibiotic, sarecycline, is in phase III trials for acne vulgaris and in phase II trials for acne rosacea. Sarecycline, “compared with existing tetracycline antibiotics, showed improved anti-inflammatory properties and a narrower spectrum of activity,” Dr. Stein Gold said.

A topical minocycline in a foam formulation shows promising results for tolerability and efficacy in phase II trials for moderate and severe acne, she added. Dapsone as a 7.5% topical gel formulation is in phase III clinical trials as well.

Another antibiotic with a long history of systemic use for acne, clindamycin, is also showing promising results in combination with benzoyl peroxide (1.2%/3.75% gel). A 12-week double-blind study of the combination, compared with vehicle alone for individuals with moderate or severe acne, showed significant improvement in comedonal and inflammatory lesions, as well as overall global improvement in severity, for the treatment arm, she said (*J Drugs Dermatol.* 2014 Sep;13[9]:1083-9).

Dr. Stein Gold reports being a consultant and investigator for Galderma, Stiefel Laboratories, and Allergan; a consultant and speaker for Valeant; a speaker for Ranbaxy Laboratories, Promius Pharma, and Actavis; and a medical/legal consultant for Roche.

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Commentary by Dr. Krakowski

THE IDEA THAT WE USE antibiotics in the treatment of acne both for their antimicrobial as well as their anti-inflammatory effect has always intrigued me. The antibiotic angle makes total sense: You have bacteria, *Propionibacterium acnes*, playing what is thought to be a causative role in the pathogenesis of acne; you kill that bacteria; the acne improves. But if you think about it from the anti-inflammatory perspective, we have much more potent anti-inflammatory medications at our disposal, and these agents are not associated with any known microbial resistance. I would love to explore how low-dose antibiotics compare with some of our more conventional anti-inflammatory medications in terms of their overall ability to impact acne at the clinical level. Maybe the data already exist within a population of adolescent rheumatology patients with acne. Perhaps one day we will be using an acne regimen that consists of something akin to benzoyl peroxide, with its well-documented antimicrobial activity, and topical NSAIDs or some immunomodulator, allowing us to completely avoid the use of systemic antibiotics.

Topical crisaborole shines in treating eczema

BY BRUCE JANCIN

AT THE EADV CONGRESS

COPENHAGEN – The nonsteroidal phosphodiesterase-4 inhibitor crisaborole aced all Food and Drug Administration–required efficacy and safety endpoints as a topical treatment for atopic dermatitis, according to results from a pair of pivotal phase III randomized trials.



DR. LEBWOHL

“This is a fairly rapidly effective treatment,” explained Dr. Mark G. Lebwohl, who presented the findings at the annual congress of the European Academy of Dermatology and Venereology. “It has a favorable safety profile and has been studied in patients as young as 2 years of age. It may represent a new, safe, and efficacious treatment for patients 2 years of age and older with mild to moderate atopic dermatitis.”

Atopic dermatitis (AD) experts have long complained of a major unmet need for new, safe, and effective topical agents for AD, a condition that affects an estimated 18%-20% of children and 2%-10% of adults. Current treatment options all have drawbacks.

Topical steroids, long a treatment mainstay, are viewed by many parents with phobic mistrust of safety. And both FDA-approved topical calcineurin inhibitors carry black box warnings of possible cancer risk.

The two pivotal phase III studies, identical in design, included a total of 1,522 patients aged 2 years through

adulthood with mild to moderate AD. Roughly 60% of patients had moderate disease, as defined by an Investigator’s Static Global Assessment (ISGA) score of 3 on a 0-4 scale; the other 40% had mild AD. The mean involved body surface area was 18%.

Participants were randomized two to one to crisaborole ointment 2% b.i.d. or vehicle for 28 days. Physicians assessed patients at baseline on day 1 of the study and again on days 8, 15, 22, 29, and 36. The primary endpoint was the proportion of patients on day 29 who had an ISGA of 0 or 1 – clear or almost clear – as well as at least a 2-point improvement from baseline on that scale.

In one of the trials, that endpoint was achieved in 32.8% of the crisaborole group, compared with 25.4% of controls.

“That 25% placebo response is actually fairly typical for atopic dermatitis studies,” according to Dr. Lebwohl, professor and chairman of the department of dermatology at Mount Sinai School of Medicine, New York.

In the other study, 31.4% of the crisaborole group and 18% of controls achieved the primary endpoint. In both studies, the difference was statistically

significant in favor of topical crisaborole.

There were two prespecified secondary endpoints. One was time to treatment success, as defined by clear or almost clear. A “striking” significant difference between the study arms appeared as early as the first assessment, just 1 week into the trial, Dr. Lebwohl observed.

The other secondary endpoint was the FDA’s former efficacy standard, which required being clear or almost clear without the additional need for at least a 2-point ISGA improvement. That endpoint was achieved by 51.7% and 48.5% of crisaborole-treated patients in the two studies, compared with 40.6% and 29.7% of controls. Again, both differences were statistically significant.

No treatment-related serious adverse events occurred in either study. Mild application-site pain was slightly more common in the crisaborole-treated patients. But the rate of study discontinuations because of adverse events was identical between the crisaborole and control groups, at 1.2%. No differences in laboratory values, ECGs, or

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Commentary by Dr. Eichenfield

MOST ATOPIC ECZEMA is managed with emollients and intermittent topical corticosteroids. While this can be effective in many children and adolescents, there is still great concern about side effects, and a huge amount of “steroid phobia” that leaves many patients treated with inadequate medication to control their disease. Phosphodiesterase-4, an enzyme important in cyclic adenosine monophosphate (cyclic-AMP) in inflammatory cells, is elevated in inflammatory cells in atopic dermatitis. Crisaborole is a boron-based PDE-4 inhibitor, designed as a topical anti-inflammatory agent, in a pathway distinct from corticosteroids. After phase II studies showing good safety and efficacy data, including a “maximal use” study on children and adolescents with high body surface area eczema involvement, large phase III trials showed statistically superior results with crisaborole ointment, compared with the crisaborole ointment vehicle, in terms of the those treated attaining the “Global Score” criteria, as well as the time to being “clear or almost clear.” With low rates of study discontinuations and good safety data, including no differences in laboratory values with the medication, these are important studies that may pave the way for approval of a new treatment for pediatric and adult eczema.

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vital signs were noted between the two groups.

Dr. Lebowhl explained that boron is an essential element in crisaborole. The boron stimulates an increase in cyclic adenosine monophosphate levels, which in turn results in a steep reduction in production of inflammatory cytokines, including interleukins-4, -2, and -31, as well as tumor necrosis factor-alpha.

One audience member asked if it's possible that crisaborole acts systemically rather than topically, given that patients averaged 18% body surface area involvement, and such a large area of damaged skin could conceivably allow the topical agent ready access to the circulation.

Dr. Lebowhl replied that systemic absorption of the drug was minor. "If you break down the results into patients with very low body surface areas – the lowest was 5% – those patients im-

proved as well. So, I think it would be unlikely that this was a systemic effect."

Anacor, which is developing the drug as a treatment for AD and other skin diseases, plans to file for marketing approval during the first half of 2016.

Anacor sponsored the two pivotal phase III randomized trials. Dr. Lebowhl declared having no financial conflicts of interest, because all funds went directly to the medical center in which he practices.

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Another promising topical for eczema

BY BRUCE JANCIN

AT THE EADV CONGRESS

COPENHAGEN – A novel topical nonsteroidal inhibitor of phosphodiesterase-4 showed a favorable efficacy to side effect ratio in a phase II study of adolescents and adults with mild to moderate atopic dermatitis, Dr.

of new topical therapies for atopic dermatitis (AD). In addition to the successful phase II study of OPA-15406 he presented, a highlight of the EADV congress was the strongly positive pivotal phase III data presented for crisaborole, another nonsteroidal topical PDE-4 inhibitor, albeit with a different mechanism of action.

tients, 70% with moderate AD, the rest with mild disease. About 20% were adolescents, the rest adults. Their mean baseline Eczema Area Severity Index (EASI) score was 9.5, with a self-reported pruritus score of 61 on a 0-100 scale. Participants were randomized to twice-daily application of OPA-15406 at 0.3% or 1% or the vehicle ointment as a control.

A significant treatment effect was seen within the first week. At 1 week, the mean EASI score was reduced by 31% from baseline in the 1% OPA-15406 group, 15% with the 0.3% formulation, and 6% with vehicle. The active treatment remained significantly more effective than vehicle throughout the 8-week period.

Another measure of efficacy – an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 along with at least a 2-point improvement on the 0-5 scale at week 4 – was met by 21% of patients on 1% OPA-15406, 15% on the 0.3% formulation, and 2.7% on vehicle. By the less stringent standard of an IGA of 0 or 1 plus at least a 1-point reduction at week 4, the success rates were 30%, 24%, and 10%.

Dr. Hanifin said the 1% formulation is the one likely to advance to phase III studies, given its superior efficacy. This was particularly evident with regard to itch. At the first evaluation, after just 1 week of treatment, pruritus scores showed a mean 30% reduction with 1% OPA-15406 versus no signif-

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Commentary by Dr. Eichenfield

OTHER TOPICAL AGENTS targeting PDE-4 are investigational ointments developed by the Japanese company Otsuka, OPA-15406. The phase II trial of ointments, 0.3% and 1%, were used twice daily for mild and moderate AD in adolescents and adults, and compared with the ointment vehicle. The study showed statistically significantly higher numbers of patients made it "clear or almost clear" and "clear and almost clear and a 2-point improvement" in the Investigator Global Assessments at week 4. Itch scores also were decreased with the 1% ointment, which is the formulation that will probably move into phase III studies.

Jon M. Hanifin reported at the annual congress of the European Academy of Dermatology and Venereology.

"For topical agents, I think a 30% improvement with few side effects is a desirable balance," observed Dr. Hanifin of Oregon Health and Sciences University, Portland.

The investigational agent, known for now as OPA-15406, is formulated as a twice-daily ointment. It is highly selective for the phosphodiesterase-4 (PDE-4) B subtype.

Dr. Hanifin noted that these are "exciting times" in the development

For Dr. Hanifin these developments are particularly satisfying personally because 33 years ago as a young investigator – before the term "translational science" had come into vogue – he and his research team made the seminal observation that increased phosphodiesterase activity is "a basic biochemical characteristic relevant to skin immunocellular regulation in atopic disease" (*J Allergy Clin Immunol.* 1982 Dec;70[6]:452-7).

The 8-week, multicenter, randomized, double-blind phase II OPA-15406 dose-ranging study included 121 pa-

Busting atopic dermatitis therapy myths

BY KARI OAKES

EXPERT ANALYSIS FROM SDEF LAS
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LAS VEGAS – In the treatment of eczema, the gap between evidence and practice can be broad.

Dermatologists who treat atopic dermatitis confront many challenges – patients may be severely atopic, have a hard time being compliant with therapies, and have frequent recurrences, Dr. Robert Sidbury said at the Skin Disease Education Foundation’s annual Las Vegas dermatology seminar. “It just is not easy,” he said.

However, even for challenging patients, physicians should be mindful of evidence-supported treatments and be attentive to practice gaps, said Dr. Sidbury, chief of the division of dermatology at the University of Washington’s Seattle Children’s Hospital.

Though the field is rapidly changing, the American Academy of Dermatology has issued practice guidelines that can help guide clinical treatment decisions, said Dr. Sidbury, who helped develop the AAD guidelines. He noted that prescribers may eventually feel the pain of the practice gap if AMA-driven performance measures are enforced.

At the meeting, Dr. Sidbury dis-



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Treating atopic dermatitis poses many challenges – patients may be severely atopic, have a hard time being compliant with therapies, and have frequent recurrences.

cussed areas in which many clinicians may have a practice gap in the treatment of eczema. Topping the list of non-evidence-based eczema care are overuse of steroids, oral antibiotics, and nonsedating antihistamines.

Practice gap: Many clinicians believe that topical steroids are more effective for atopic dermatitis when used twice daily.

Reality: “Randomized, controlled trials and a systematic review suggest

that there is no benefit to twice-daily use of steroids,” over once-daily use, Dr. Sidbury said, though he admitted that he’s having a hard time breaking his own longstanding practice habit of prescribing twice- rather than once-daily dosing of topical corticosteroids. He pointed out that Dr. Hywel Williams, the director of the University of Nottingham’s (England) Center of Evidence-Based Dermatology, calls this

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icant change in controls. He added that his clinical impression is that many patients experience a significant improvement in itching within the first 24 hours on the 1% formulation, an observation that deserves formal study.

Scores on the Dermatology Life Quality Index and Children’s Dermatology Life Quality Index were significantly better in the active therapy arms than with vehicle as early as week 1.

The adverse events findings were “not very exciting,” according to the dermatologist. No treatment-related serious adverse events occurred. The two most common adverse events



DR. HANIFIN

leading to treatment discontinuation – worsening AD and pruritus – occurred more often in the vehicle-treated controls.

Session cochair Dr. Jacek Szepletowski called the pruritus results particularly impressive.

“It’s very difficult to do successful clinical trials of topicals for atopic dermatitis because the vehicle alone, especially if it’s an ointment, can have favorable effects which increase over time both on EASI and pruritus,” commented Dr. Szepletowski, professor and head of the department of dermatology, venereology, and allergology at the Medical University of Wroclaw (Poland).

The study was sponsored by Otsuka Pharmaceuticals. Dr. Hanifin reported serving as a consultant to and paid investigator for the company.

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the “lowest-hanging fruit” in terms of cost savings, safety, and convenience to patients.

Practice gap: Unnecessary skin cultures can lead to overuse of systemic antibiotics in atopic dermatitis.

Reality: Colonization with *Staphylococcus aureus* occurs in more than 90% of adults with atopic dermatitis, but the vast majority of these patients are

for Performance Improvement nearly passed an overuse measure that would have penalized the prescription of nonsedating antihistamines in this setting, he said.

Practice gap: Systemic immunomodulatory therapy is used for pediatric atopic dermatitis, despite the lack of data that provide clear guidance.

Reality: The landscape here is a little more complicated, according to Dr. Sidbury. Among the systemic immuno-

kg per day, divided into twice daily dosing. The maximum dose is 300 mg/day, and the microemulsion form is preferred. Overall, mycophenolate is the best-tolerated immunosuppressive. If methotrexate is chosen, it should be dosed at 0.2-0.7 mg/kg per week; liver function should be checked at 5-7 days after dosing, since methotrexate can cause a transient transaminitis. There are no standard recommendations to guide if or when to do liver biopsy recommendations in children receiving methotrexate (J Am Acad Dermatol. 2014 Aug;71[2]:327-49).

Practice gap: Eczema appointments may last only 10-20 minutes.

Reality: “Proper eczema education takes much longer,” Dr. Sidbury said. Among patients and clinicians, there is still “rampant misinformation,” with persistence of fundamental knowledge gaps. “Studies repeatedly validate the role of education” in providing optimal care for eczema sufferers and their families, he emphasized (Pediatr Allergy Immunol. 2015 Jan 23. doi: 10.1111/pai.12338).

How is a busy physician to integrate all of these recommendations into practice and make sure patients are getting proper education? “Don’t reinvent the wheel – Google it!” Dr. Sidbury said. Resources from the National Eczema Association, among others, can help guide care. Eczema action plans that can be downloaded provide a roadmap for shared decision making; food allergy clinical practice guidelines help patients avoid allergens, and patients can further their knowledge when directed to reputable websites like the National Eczema Association and resources like www.eczemacenter.org, at Rady Children’s Hospital–San Diego.

Dr. Sidbury disclosed that he was a site principal investigator for an Anacor Pharmaceuticals–sponsored trial of a new topical anti-inflammatory agent for allergic dermatitis, and that he is on the Scientific Advisory Committee of the National Eczema Association.

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Commentary by Dr. Eichenfield

THIS ARTICLE SUMMARIZES some great “pearls” on atopic dermatitis therapy from Dr. Robert Sidbury, professor of pediatrics and chief of the division of dermatology at the University of Washington’s Seattle Children’s Hospital. Dr. Sidbury was a cochair (along with myself) of the American Academy of Dermatology Task Force for Guidelines for Atopic Dermatitis, and he blends great knowledge of the evidence basis behind therapeutic suggestions with practical experience. His identifications of “practice gaps,” “realities,” and translation to recommendations are pithy, salient, and important. While the talk was directed to dermatologists, the information is totally relevant for pediatricians and any health care practitioners assisting with AD care.

not infected. “Except for bleach baths in concert with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with atopic dermatitis,” Dr. Sidbury said.

“How do we know when eczema is infected? We know it when we see it. You are best served by using your clinical gestalt,” he added. Eczematous skin presents along a continuum, ranging from erythema, scaling, and crusting, to a frankly purulent appearance with clear infection, and clinical presentation and judgment should guide treatment. Barring frank infection, the evidence doesn’t support use of systemic antibiotics (Br J Dermatol. 2010 Jul;163[1]:12-26).

Practice gap: Many patients with atopic dermatitis receive nonsedating antihistamines for itching.

Reality: There is no evidence that nonsedating antihistamines are beneficial unless the patient has concurrent rhinoconjunctivitis, so data don’t support their use “for the actual itch of eczema,” Dr. Sidbury said. In fact, the AMA-sponsored Physician Consortium

suppressants, cyclosporine, methotrexate, azathioprine, and mycophenolate have the most evidence backing their use. However, there remains a lack of comparative studies and a lack of studies evaluating these therapies in the pediatric population, he said.

In general, Dr. Sidbury said that systemic therapy for atopic dermatitis is indicated only when control is inadequate despite truly optimized topical care, and the condition is having a “significant negative physical, psychological, or social impact” on the patient. Before beginning these potent systemic therapies, it’s important to assess that the patient and family are truly adherent to the topical treatment regime, and that adjunctive treatments like wet wraps and strict allergen avoidance are being followed. The Food and Drug Administration is beginning to include pediatric patients in clinical trials of systemic therapy for atopic dermatitis, so the quality of data should improve.

If systemic therapy is initiated, some clinical pearls can guide use, he said. Cyclosporine has the quickest onset of action and can be dosed at 3-6 mg/

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Expert shares treatment tips for molluscum contagiosum and warts

BY DOUG BRUNK

EXPERT ANALYSIS AT PDA 2015

PARK CITY, UTAH – In her practice as a pediatric dermatologist, Dr. Sheryll L. Vanderhooft sees her share of children who present with molluscum contagiosum and warts.

At the annual meeting of the Pacific Dermatologic Association, she shared her approach to caring for patients who present with these two common conditions.

The root cause of molluscum contagiosum is a poxvirus infection that spreads by skin-to-skin contact. It takes an average of 6 months to 2 years for the host immune response to occur. “During that time parents panic and some need a lot of hand-holding,” said Dr. Vanderhooft, professor of pediatric dermatology at the University of Utah School of Medicine, Salt Lake City. “They seek treatment primarily due to associated dermatitis triggered or exacerbated by the virus. There’s also the risk of spreading the condition to other children and the stigma of visible lesions.”

No FDA-approved therapies for molluscum contagiosum currently exist. “There are many options, but

none of them are guaranteed to hasten resolution,” she said. “This is a very important point to deliver to parents before you start trying to do a lot of therapy.” Common treatment options are cryotherapy and cantharidin destruction, curettage, treatment with



DR. VANDERHOOF

topical imiquimod or retinoids, oral cimetidine, and injections of *Candida* antigen.

According to two retrospective studies of *Candida* antigen injection, complete clearance occurred in 56% of patients after an average of three

treatments, while partial clearance occurred in 28%-38% of patients after an average of four treatments (*Pediatr Dermatol.* 2008;25:189-92; *Pediatr Dermatol.* 2011;28:254-8). The main side effect was local pain from the injections.

Antiviral and antitumor effects are seen with imiquimod cream through activation of the innate immunity and upregulation of cytokines, such as interferon-alpha, Dr. Vanderhooft said. It’s FDA approved for genital and perianal warts in patients older than 12 years of age, as well as for actinic keratosis, superficial basal cell carcinoma, and antiviral-resistant herpes simplex virus in patients older than 12 years of age. In a prospective study, researchers compared imiquimod cream five times per week up to 16 weeks, with cryotherapy for the treatment of molluscum contagiosum in children (*Pediatr Dermatol.* 2010;27[4]:388-94). More than half of patients (60%) achieved clearance by week 6 and 92% achieved clearance by week 12. There were no relapses observed at 6 months. “Liquid nitrogen cleared the lesions faster, but caused more postinflammatory dyspigmentation, and there were a few re-

Commentary by Dr. Krakowski

THE TREATMENT STRATEGIES for molluscum contagiosum are well documented in the literature. What is not well researched or discussed is what to do with the “associated dermatitis triggered or exacerbated by the virus.” Multiple dermatitis patterns have been documented, ranging from inflammation of individual molluscum lesions to an eczema-like rash circumscribing the molluscum lesions to a disseminated Gianotti-Crosti-like reaction pattern.

So, do you treat the molluscum first or do you treat the dermatitis? That is a tough question: Many of the treatments we use to help expedite the resolution of molluscum rev up the immune response against the pox virus that causes the lesions in the first place; on the other hand, many of the treatments we would use for any dermatitis present lower the cutaneous immune response in

order to calm inflammation. So, you have some theoretical contradictions to consider: Do you risk spreading the molluscum lesions by using a topical steroid in the area where a dermatitis exists or do you ignore the distress your patient is in secondary to that dermatitis?

I usually treat the individual molluscum contagiosum lesions with topical cantharidin. If a symptomatic dermatitis is present, I will do a careful exam to make sure that a true infection from the lesions is not present (abscess or cellulitis); if not, I will then instruct the families to use a moderate strength topical steroid on the areas removed from any active molluscum. I also instruct the patients to keep nails trimmed, so that any skin barrier trauma and subsequent spread of the pox virus is minimized. In this case, caregiver education and anticipatory guidance play crucial roles in the successful management of this condition.

lapses in this group,” Dr. Vanderhooft said.

The downside to imiquimod treatment is that it requires prolonged use, it’s expensive, “and a lot of insurance companies will not pay for it because it’s not FDA approved for young children,” she said. “It can also cause irritant dermatitis, which is a difficult problem when you already have a kid who may be atopic and you’re trying to treat molluscum.” Also, according to the package insert for Aldara cream, imiquimod administered three times per week for 16 weeks was not shown to be superior to vehicle alone in two randomized, controlled trials that were completed in 2006 but never published. There were 323 children in one study, with complete clearance at 18 weeks in 24% of children treated with imiquimod, compared with 26% of children treated with vehicle alone. There were 379 in the second study with complete clearance in 24% and 28% of children, respectively.

Children who were treated with imiquimod in these two studies were more likely to experience application site reactions, otitis media, and conjunctivitis. In addition, a pharmacokinetic study of 22 children with molluscum involving at least 10% of body surface area showed systemically detectable drug levels after single and multiple doses three times a week for 4 weeks. The findings from these three studies led to changes in the FDA-approved package insert in 2008. Section 1.4 of the “indications and usage” section of the package insert now reads: “Aldara cream has been evaluated in children ages 2-12 years with molluscum contagiosum and these studies failed to demonstrate efficacy.” With that in mind, Dr. Vanderhooft’s recommendation “is to either stop prescribing it in children or prescribe it once daily or twice daily as tolerated, not every other day.”

While molluscum contagiosum is caused by a poxvirus, warts are growths on the skin caused by infection with human papillomavirus (HPV). On average, 75% of children will develop immunity to HPV within 3 years, “whether you do nothing, or whether you try to treat it,” she said.

“Parents seek treatment when they are large, spreading, or causing social stigma. There are many treatment options, but none are guaranteed to hasten resolution. This needs to be driven home to patients when you’re counseling them.” Numerous treatment



COURTESY DR. SARAH CIPRIANO

There’s a risk of spreading molluscum contagiosum to other children by skin-to-skin contact.

options exist, ranging from destruction with cryotherapy and pulsed-dye laser to salicylic acid and various topical or injectable agents. The only FDA-approved option is imiquimod cream, which is approved for genital and perianal warts only in patients 12 years of age and older.

In Dr. Vanderhooft’s experience, Candida antigen injections benefit some patients. After injection of 0.3 mL of Candida antigen into one or two warts at monthly intervals, researchers in one study observed complete clearance in 87% of patients after an average of 3.5 treatments, while 7% demonstrated no improvement after an average of 3.75 treatments (*Pediatr Dermatol.* 2008;25:189-92).

Zinc supplementation is another option, she said. In a randomized trial, researchers who evaluated oral zinc supplementation versus placebo for 2 months found complete clearance in 20 out of 23 patients in the treatment group (87%), compared with none of the 20 patients in the placebo group (*Br J Dermatol.* 2002; 146[3]:423-31).

All patients in the zinc group reported nausea. “That’s what has limited zinc therapy in my patient population,” Dr. Vanderhooft said.

In a more recent study, researchers conducted a placebo-controlled study of zinc sulfate 10 mg/kg per day up to 600 mg per day for up to 2 months (*J Am Acad Dermatol.* 2009;60[4]:706-8). Complete clearance of all warts was achieved in 78% of patients in the treatment group, compared with 13% in the placebo group. No recurrence of warts was observed at the 6-month follow-up.

Topical fluorouracil (5-FU) for warts has also been evaluated. One study of once- or twice-daily application of 5-FU under occlusion for 6 weeks demonstrated improvement in 88% of patients, including 13% with complete clearance (*Br J Dermatol.* 2011;165[2]:233-46). No blood levels of the drug were detected. “It’s thought to be safe and well tolerated, but over-the-counter salicylic acid has better efficacy and is quite a bit cheaper,” Dr. Vanderhooft said.

Another strategy for recalcitrant warts involves administration of squaric acid dibutyl ester (SADBE). In a recent retrospective chart review conducted over a 10.5-year period, researchers evaluated 72 children with recalcitrant warts who had failed therapy with multiple agents and were followed for a period of 6 months to 11 years (*Pediatr Dermatol.* 2015;32:85-90). The protocol involved sensitizing the children to 2% SADBE. The treatment then started 2 weeks later, with 0.4% SADBE applied three times per week initially, with an extra day added per week as tolerated to reach daily use if possible. The researchers found that 40 of the 48 (83%) patients in whom treatment outcomes could be obtained reported complete resolution of their warts. Seventy percent of patients used a maximum concentration of 0.4% SADBE and 60% of patients reported no adverse effects. The average time to reduction in size of warts was 2.6 months after sensitization, and treatment continued for a mean of 8 months.

Dr. Vanderhooft reported having no financial disclosures.

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Cut simple carbs to clear acne

BY AMY KARON

AT WCD 2015

VANCOUVER – Mounting evidence suggests that consuming a low glycemic index diet can substantially improve acne, according to Dr. Hyuck Hoon Kwon.

The approach has held up in several small-scale randomized clinical trials, earning it a grade of 1B last year from the American Academy of Dermatology, noted Dr. Kwon of Seoul (South Korea) National University.

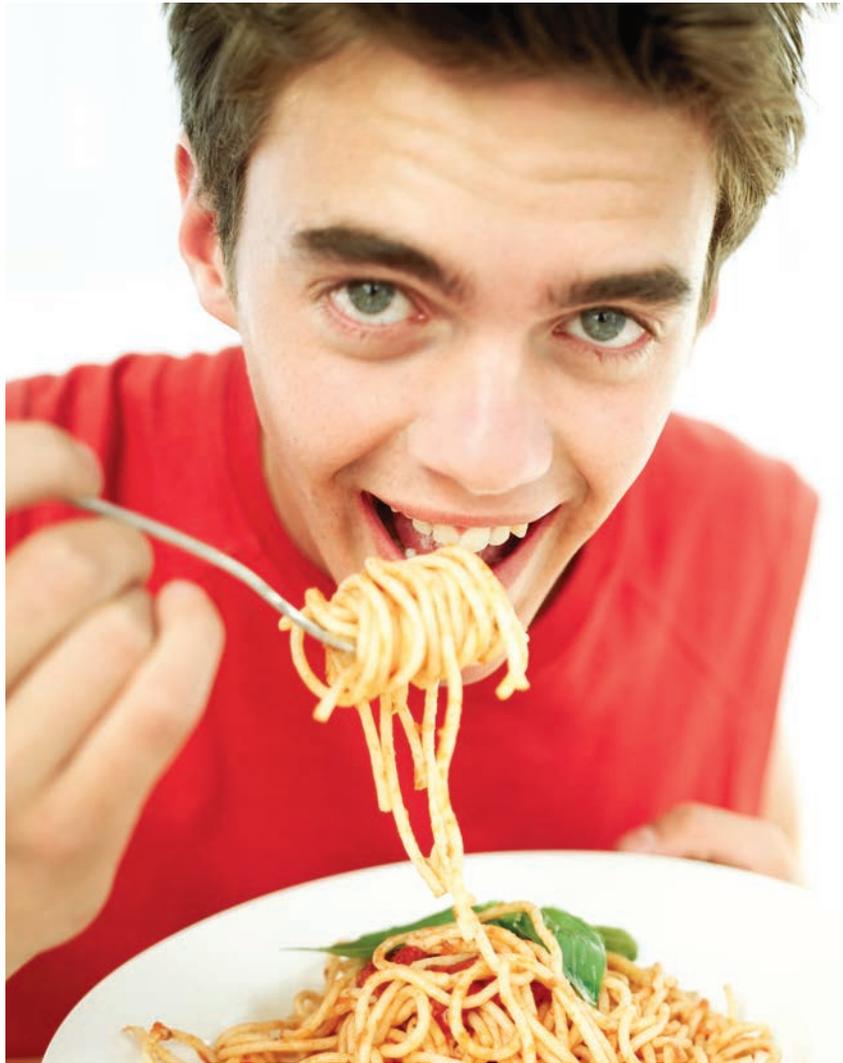
“Dermatologists can recommend dietary modification to patients, and can advise them to avoid foods that they believe worsen their acne,” Dr. Kwon said at the World Congress of Dermatology. He said he has seen clinically meaningful reductions in acne lesions as soon as 4 weeks after patients cut their intake of refined carbohydrates and other high glycemic index (GI) foods, although results can take up to 12 weeks, and more studies of time to effect are needed.

Scientists and clinicians have long debated the role of diet in the pathogenesis of acne, and until recently, there were no randomized, controlled trials or meta-analyses of the topic. But observational studies have repeatedly documented “astonishingly” low rates of acne in cultures with “traditional” diets that are lower in refined carbohydrates and fat than typical Western fare, said Dr. Kwon.

In one study of 1,285 individuals in Korea, those who did not have acne reported consuming significantly higher amounts of fish and yellow, leafy green, and cruciferous vegetables, while those with acne ate significantly more instant noodles, processed cheeses, and “junk” foods, he noted (*Eur J Dermatol.* 2010;20:768-72).

In another trial, Dr. Kwon and colleagues randomized 32 individuals with mild to moderate acne to either a low-GI diet that emphasized beans, barley, vegetables, fish, and whole-grain breads, or to a high-GI control

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Commentary by Dr. Krakowski

THE ROLE OF “DIET” in acne has long been investigated. We hear all the time, in the clinics, “Doc, tell my son to stop eating pizza so his face gets better” or “I think my daughter is drinking too much chocolate milk.” The studies referred to in this article are interesting in that they seem to support the increasingly popular notion that a low glycemic index diet might be associated with less acne. I would not say I am absolutely convinced yet of this association; quite simply, we need more rigorous, well-designed, prospective trials to help elucidate the answer. However, this discussion is certainly intriguing, especially in light of the fact that there is a molecular mechanism that could correlate with the purported clinical response. At a minimum, caregivers must be familiar with this body of literature to have an intelligent discussion with patients and their families. A low glycemic diet has additional health benefits, so I usually promote it as part of an overall healthy lifestyle anyway. Strict avoidance diets, however, may not be safe, and patients need to be educated to work in concert with their providers, so that everyone is on the same page.

Continued from previous page

diet (*Acta Derm Venereol.* 2012;92:241-6). The low-GI group ate more protein to replace calories lost from cutting carbohydrates. At 10 weeks, the groups had similar mean calorie intakes and body mass indexes, but the low-GI group had reduced its dietary glycemic load from baseline and had significantly fewer inflammatory and noninflammatory acne lesions compared with

baseline and with the high-GI group, Dr. Kwon said. The low-GI group also had significant decreases in total average area of sebaceous glands, and decreased expression of sterol response element-binding protein-1 (SREBP-1), which stimulates lipogenesis in sebocytes.

Most recently, scientists have explored the molecular mechanisms linking diet to acne, Dr. Kwon noted. High GI diets trigger chronic hyperin-

sulinemia, which impairs the ability of FoxO1 transcription factor to mediate androgen receptor signaling, oxidative stress, lipogenesis, and sebaceous gland homeostasis. Importantly, FoxO1 inhibition also is associated with activation of mTORC1, which promotes lipid and protein synthesis, sebaceous gland hyperplasia, and sebaceous lipogenesis.

Dr. Kwon reported having no relevant conflicts of interest.

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Beware common management pitfalls in severe refractory pediatric atopic dermatitis

BY JENNIE SMITH

EXPERT ANALYSIS FROM 2015
AAAAI ANNUAL MEETING

HOUSTON – Dermatologists, allergists, and other physicians treating children with extremely refractory forms of atopic dermatitis (AD) must be aware of common treatment and management pitfalls before jumping to immunosuppressant or biologic therapies, says pediatric eczema researcher Dr. Donald Y.M. Leung, particularly as this is a patient group for whom no systemic therapies have been approved.

In a presentation at the annual meeting of the American Academy of Allergy, Asthma, and Immunology, Dr. Leung shared insights from his clinical experience at National Jewish Health in Denver, whose pediatric eczema program represents a national referral center for patients with severely refractory disease and their families.

“As managed care continues to march on, you will be faced with taking care of the more difficult patients,” Dr. Leung told clinicians. “You will see all forms of AD in clinical practice, therefore one size does not fit all, and a stepwise approach is needed to [treat] the different forms of eczema.”

Clinicians first need to determine what step, or grade, of eczema a patient has. For example, step 2 and 3 eczema is characterized by moderate disease not controlled by intermittent



“You will see all forms of AD in clinical practice, therefore one size does not fit all, and a stepwise approach is needed to [treat] the different forms of eczema,” Dr. Donald Y.M. Leung said.

use of topical steroids or calcineurin inhibitors.

National Jewish Health’s day-based program aims to first clear up children presenting with severe eczema before clinicians attempt diagnostic testing. This is achieved through the use of wet wraps, until skin has healed enough for testing to begin.

With wet wraps and day hospitalization, “you can go from severe to mild within a few days,” Dr. Leung

said. For children who do not improve after the wet wraps, ruling out immune deficiency or other diagnoses is key. Dr. Leung and colleagues look for Dock 8 (dedicator of cytokinesis 8) protein deficiency in children who fail to respond to wet-wrap treatment, especially if they have presented with recurrent herpes infections or persistent warts.

Another important function of

Continued on following page

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the day program is to observe how parents manage children with eczema. Many, Dr. Leung said, turn out to be noncompliant with recommendations on bathing and medications, often because of the discomfort it causes the child. The monitoring is essential to reveal errors in care. “You can’t tell this in a 10-minute office visit,” he said.

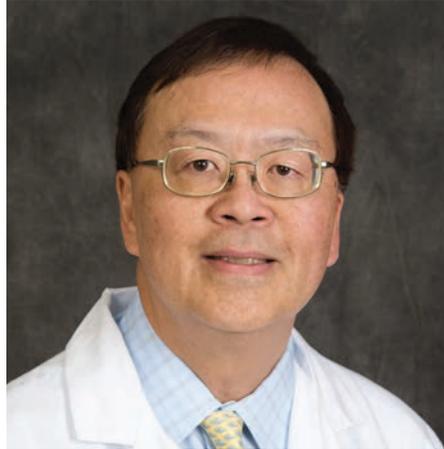
A top reason children fail therapy, he said, is because parents misinterpret recommendations on applying medicine after bathing. Many think that after applying a topical medication, “you can get better absorption if you put the moisturizer on top of the topical steroid. That really just dilutes the medication and you get ineffective therapy.”

Another upshot of the monitoring is that clinicians can identify parents suffering from depression, stress, or financial problems that prevent them from complying. “As with asthma, psychosocial factors loom big,” he said. Parents are extensively counseled and referred as needed, he said. Children also can be trained not to scratch their skin, and children over 5 years in the eczema program are offered hypnosis and biofeedback training to learn how to control their response to itching.

When taking a history of suspected food reactions, Dr. Leung said, it’s important to note that only hives and anaphylaxis are clearly linked to food allergy. “Skin testing and blood work

is what we all do, but that’s helpful only if negative. If it’s positive, it still doesn’t tell you that they have food-induced eczema, and like it or not, some form of the food challenge is necessary.”

Dr. Leung said it is appropriate to conduct some oral food challenges un-



DR. LEUNG

blinded after a negative test. “If a test is positive, and the parent insists that this food may cause eczema, it’s often necessary to do a double-blind, placebo-controlled test,” he said, which is the gold standard.

In discussing systemic therapies, Dr. Leung noted that general immunosuppressants were an approach favored by dermatologists, but urged caution with regard to interferons, mycophenolate, methotrexate, azathioprine, and cyclosporin A. “These are expensive thera-

pies not approved in children, and you really need very good documentation that they’ve failed other forms of therapy before you’d move to that,” Dr. Leung said.

Oral steroids should be avoided. “I have seen thousands of cases of severe eczema, and I’ve never put somebody on oral steroids unless they happened to have an asthma exacerbation concurrent with AD,” he said. “This is because they often have rebound within a week of stopping oral steroids, and that rebound can be worse than the disease you started with.”

If oral steroids must be used, “you should taper slowly and increase the intensity of skin care, so they don’t have a severe rebound.”

Dr. Leung said that while omalizumab should work in any disease with an elevated serum IgE level, “more often than not it doesn’t,” and it probably should be reserved for patients with a very clear history of allergen-induced eczema, underlying urticaria, or other forms of respiratory allergy that may be triggering asthma.

Two potential approaches in which allergists and dermatologists can work together, Dr. Leung said, are phototherapy and allergy immunotherapy. The latter is controversial in AD, he acknowledged, “but if somebody has mainly dust mite allergy or is monosensitized, it’s more likely you will get good benefit. If they’re polysensitized, it is unlikely because it’s mainly a barrier problem.”

Dr. Leung did not recommend antibiotics except in the case of overt *Staphylococcus aureus* infection, so as not to select for methicillin-resistant *S. aureus* (MRSA). “If you’re going to treat with some regimen, keep in mind that staph comes from the nose; that’s the body’s reservoir. You should always use an intranasal Bactroban [mupirocin] along with a systemic antibiotic.” Effective eradication of MRSA infection requires more drastic measures, including treatment of other family members and pets.

Dr. Leung disclosed doing consulting work for Celgene, Novartis, Regeneron, and Sanofi-Aventis, and a research grant from Horizon Pharma.

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Commentary by Dr. Eichenfield

DR. DONALD LEUNG has done great work in advancing the field of atopic dermatitis with a broad set of important basic science and translational research, as well as in his work at National Jewish Health and its superb eczema program. This article highlights the more severe atopic dermatitis patients, and the steps that might be considered to aggressively manage AD before the utilization of systemic immunosuppressive agents. Important takeaways:

- » He doesn’t use oral corticosteroids for AD.
- » Wet wraps (topical corticosteroids applied to wet skin and covered with wet wraps for overnight or several hour applications) can “break” the eczema cycle in severe patients and bring them to mild AD in a few days.
- » Much failure in efficacy is underuse of medications both because of nonadherence or poor understanding of how (and how much) to use.
- » Phototherapy and allergy immunotherapy (although controversial) may be helpful in difficult cases.

Severe diaper rash, cradle cap raise suspicion for pediatric psoriasis

BY M. ALEXANDER OTTO

EXPERT ANALYSIS FROM SDEF WOMEN'S AND PEDIATRIC DERMATOLOGY SEMINAR

NEWPORT BEACH, CALIF. – A history of severe cradle cap and diaper dermatitis helps to differentiate between pediatric psoriasis and atopic dermatitis, so be sure to ask, according to Dr. Alan Menter, chief of the dermatology division at the Baylor University Medical Center in Dallas.

“Both are markers for later onset of psoriasis, and are much more likely to be a marker for psoriasis than atopic eczema,” he said at Skin Disease Education Foundation’s Women’s & Pediatric Dermatology Seminar.

The tip to ask about cradle cap and diaper dermatitis is based largely on clinical observation, but is more useful than asking about a family history of psoriasis, because people tend to keep psoriasis to themselves, he noted; fam-

“Both are markers for later onset of psoriasis, and are much more likely to be a marker for psoriasis than atopic eczema.”

ily members and even spouses might not know. “It’s a very hidden disease, so family history is of little benefit,” he said.

Recent strep infection also may provide a clue, not only for guttate psoriasis but also probably for plaque psoriasis in children, Dr. Menter said. But the sooner pediatric psoriasis is caught and controlled, the better, no matter how it is detected. Aside from the suffering it causes on its own, psoriasis in children has been linked to diabetes, hypertension, fatty liver disease, obesity, and cardiovascular problems, he noted.

Commentary by Dr. Eichenfield

DR. ALAN MENTER, one of the world’s great psoriasis experts, stresses that pediatric psoriasis can be tricky to appreciate in early life, and that it can be mistaken for “cradle cap” and diaper dermatitis. Strep infections can trigger psoriasis, especially the guttate form, and overlap with Crohn’s disease can be considered as well. The major message of the article is that psoriasis can have a huge impact to the affected patient, both emotionally, psychologically, and with medical comorbidities such as obesity, hypertension, fatty liver disease, and atherosclerotic heart disease in early adulthood. In fact, studies have shown early changes in lipoproteins and cholesterol-processing abilities in children with psoriasis (*J Invest Dermatol.* 2016 Jan;136[1]:67-73). Dr. Menter makes the argument for early and aggressive intervention for pediatric psoriasis.

The mechanism of action for these comorbidities remains under investigation. Perhaps mothers with psoriasis gain more weight during pregnancy, and their children are heavier at birth, Dr. Menter said.

Crohn’s disease is far more likely in children with psoriasis, too. Dr. Menter noted that he has had referrals where the diagnosis has been missed, even in the setting of long-standing fatigue and diarrhea. “We have to look for it [Crohn’s] in our psoriasis population,” he said.

Children with psoriasis are often teased, taunted, and bullied, sometimes as young as kindergarten age. The emotional stress, loneliness, and depression can have a major impact on school and social growth, Dr. Menter said.

“Treatment of these kids goes beyond prescribing a topical steroid; they need [both] physical and psychological support,” he emphasized. Talk to parents and teachers about how the child is doing in school and other social settings. Parents might know about grades, but not much about their child’s social interactions. To help catch problems, also “take a quality of life index on all your patients with psoriasis,” he said.

It’s important to intervene early and

get children’s skin cleared quickly. “[Although] we’d love to treat [everybody] with topicals and wet compresses,” effective treatment sometimes means systemic therapy, he said.

Cyclosporine is a valid rescue option, particularly for more inflammatory disease. “Rarely, if ever, have I seen any hypertension or serum creatinine issues,” Dr. Menter said. “You just have to warn parents to be careful about gums, because you can get gingival hyperplasia, and girls don’t like the mild hypertrichosis you sometimes get around the temples and forearms,” he said.

Etanercept is another option. It’s not approved for pediatric psoriasis, but if you try hard enough, you can get insurance companies to cover it, Dr. Menter said. “You have to talk about quality of life and how psoriasis has impacted schooling,” among other topics, he explained.

Clinicians looking for child-oriented resources and support materials can recommend the National Psoriasis Foundation to their patients, he noted.

SDEF and this news organization are owned by Frontline Medical Communications.

Dr. Menter disclosed financial relationships with Abbott, AbbVie, and numerous other companies.

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Severe acne responds to fixed-combo gel

BY DENISE FULTON

EXPERT ANALYSIS FROM SDEF
HAWAII DERMATOLOGY SEMINAR

A convenient, once-daily fixed combination of 0.3% adapalene plus 2.5% benzoyl peroxide gel significantly improved lesion counts over the course of 12 weeks in patients aged 12 years and older with moderate or severe acne.

Investigators enrolled just over 500 patients from 31 sites in the United States and Canada. About half of patients were rated as having severe acne and half as having moderate acne on the investigator's global assessment (IGA) scale, Dr. Linda F. Stein Gold said at the Hawaii Dermatology Seminar provided by Global Academy for Medical Education/Skin Disease Education Foundation.

Patients were randomized to three treatment groups: adapalene 0.3%/benzoyl peroxide 2.5% gel (A-BPO-0.3%), adapalene 0.1%/benzoyl peroxide 2.5% (A-BPO-0.1%), or vehicle. Patients in each group had approximately the same total lesion count, and about half in each group had truncal acne lesions, said Dr. Stein Gold, director of clinical research in the department of dermatology at

Henry Ford Hospital, Detroit.

Patients were instructed to use their study medications once daily at night after washing with a provided cleanser. They were provided with a standardized moisturizer and cleansers.

Treatment with A-BPO-0.3% was judged as successful (IGA of 1 or almost clear) at 12 weeks in 31% of patients with severe acne. By contrast, 13.3% of patients with severe acne were judged as almost clear. In patients with severe acne, A-BPO-1% was not statistically superior to vehicle (*J Drugs Dermatol.* 2015 Dec 1;14[12]:1427-35).

"Topical treatment is still the cornerstone of acne therapy, and it is great to have additional options, especially for our more severe acne patients," Dr. Stein Gold said.

Patients noted dryness, scaling, erythema, and stinging/burning with A-BPO-0.3%, especially between weeks 1 and 2.

Dr. Stein Gold disclosed that she serves as a consultant and scientific advisory board member to Galderma, which markets A-BPO-0.3% as Epiduo Forte.

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Commentary by Dr. Krakowski

THIS IS A FAIRLY LARGE, well-designed, multicenter study. The topical treatment being evaluated utilizes the same concentration of benzoyl peroxide that is used in some of the most popular (and most expensive) over-the-counter "systems." The product adds topical adapalene 0.3%, a retinoid known for its relative tolerability and efficacy. Consequently, patients get the benefit of two tried and true acne treatments in a very convenient once-daily dosing regimen. They also get the benefit of decreased antimicrobial resistance through the concurrent use of benzoyl peroxide. I use the expected dryness, scaling, and erythema between weeks 1 and 2 as a gauge as to whether my patients are actually using the medication and then as a teaching point that "something good is happening in the skin."

Truncal acne is notoriously difficult to treat, especially when using topicals alone over such a large surface area. The practicality of reaching the affected areas and side effects like local irritation can interfere with adherence to the treatment regimen. I would like to learn more about how this product did within this specific population against the other treatment arms. For the patients who can afford it, this product may help simplify complicated acne regimens by combining two therapies into one. In an adolescent population in which you never know how a product is actually being used – if at all! – this particular treatment approach may help increase adherence and, in turn, improve clinical outcomes. The fact that this topical medication did well even in a population of patients with moderate and severe acne seems very promising.



Ask teens with acne about whey protein

BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE
SOUTH BEACH SYMPOSIUM

MIAMI BEACH – Acne on the face and trunk in adolescents could be associated with the use of whey protein supplements, according to Dr. Jonette E. Keri.

Teenage boys, especially, may use whey protein supplements in an effort to increase muscle mass or gain weight, Dr. Keri of the University of Miami said at the South Beach Symposium.

She cited a 2012 case series of five male teenage athletes aged 14-18 years who were using whey protein shakes or reconstituted powder. The teens presented with moderate to severe acne that responded poorly to standard treatment, but four of the five experienced clearing of the acne upon discontinuation of the whey protein supplement.

All five had been treated unsuccessfully with traditional therapies, including oral antibiotics, topical retinoids, and benzoyl peroxide. One teen stopped using the whey protein immediately after being counseled to do so, and he experienced improvement. Two teens didn't stop using whey protein immediately but experienced improvement in their acne when they did discontinue it. Another teen experienced clearing after discontinuing the whey protein during a second course of isotretinoin therapy, and the fifth was lost to follow-up (*Cutis*. 2012;90:70-2).

One of the teens who cleared after discontinuing the whey protein experienced a flare of the acne when he reinitiated supplementation, Dr. Keri said.

Three of the boys were trying to build muscle for football and two were trying to gain weight, which underscores the importance of asking teens about supplement use, she noted, adding that, importantly, it's not just boys who are affected.

In fact, a Brazilian study of 30 patients showed a very strong association between the onset or exacerbation of acne and initiation of whey protein use – and the finding was more pronounced among women than men,



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and among those without a personal or family history of acne (*An Bras Dermatol*. 2013;88:907-12).

In that study, subjects were examined on three occasions and followed for 60 days. “They went the gym, wanted to work out a little bit and get bigger, took some whey, and broke out in acne,” Dr. Keri said.

Although acne breakouts won't happen to everyone who uses whey protein, it's something worth considering in teens, particularly if they fail to respond to standard therapies, she said.

Although the reason for the associa-

tion hasn't yet been “teased out,” whey protein is derived from cow's milk, and it appears to be related to activation of the insulin cascade, explained Dr. Keri.

Dr. Nanette B. Silverberg of the Mount Sinai Health System, New York, author of the case series involving the five male athletes, noted that milk is known to be associated with acne and suggested that whey protein may be the fraction of dairy products that promote acne formation.

Dr. Kerri reported having no relevant disclosures.

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Commentary by Dr. Krakowski

THE CASE SERIES cited here speaks to some of the challenges that we as pediatricians and pediatric dermatologists face when partnering with our adolescent patients. Although I am not blown away by the suggestion that stopping whey protein will cure acne, I am intrigued by an underlying notion that this article points out: Teenagers may be using a host of products – whey protein included – that they simply fail to tell us about because they do not think of them as medically relevant. The onus is on us to ask. Whey protein is generally considered safe when used appropriately, but how many times a day do you think it happens that a teenager says, “If one scoop of this stuff builds muscle, then three scoops will get me ripped!” At higher doses, whey protein may be associated with liver damage, kidney dysfunction, and even an increased risk of bone fracture (especially relevant in a population prone to participating in sports). Chronic use of whey protein would be particularly important to discover in a population using isotretinoin, for example, because of that medication's potential to exert an additive and possibly even synergistic effect on organs like the liver and kidney.

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