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What's New in Atopic Dermatitis in Children 0-2 Years Old?

Report from a symposium at the 2017 World Congress of Pediatric Dermatology.

Expanscience Laboratories gathered world leaders in the field of atopic dermatitis for a symposium at the 2017 World Congress of Pediatric Dermatology in Chicago. Ahead is a summary of key points from the presentation.

UPDATE ON THE PATHOPHYSIOLOGY OF AD

BY AMY PALLER, MD

Atopic dermatitis (AD) affects 10 to 25 percent of children of all races and ethnicities. Diagnosis and effective management of the disorder is of particular concern in individuals younger than two, as 45 percent of those who develop AD will do so within the first six months of life; 60 percent of those affected will develop AD by age one.

The incidence of AD has been increasing. The prevalence is particularly increased in industrialized countries, and it parallels the increase in rates of asthma around the globe. As physicians who care for children with AD, we recognize that it is often a chronic, relapsing disorder that has some typical age-specific morphology and distribution. Particularly in the zero-to-two-year-old age group, involvement of the face is common. Sometimes extensor involvement is more common than is seen in older patients. Pruritus is one of the most troubling symptoms of AD, particularly in children. We also recognize that the condition has a profound effect on the quality of life of pediatric patients and their families.

There is a large unmet need for improved atopic dermatitis therapy, especially in younger children. Rather than treat flares, we would much rather prevent them. Some topical steroids are approved for use in patients under two years of age, and many therapies are used off-label in this group. While off-label use is certainly permissible, prescribers would prefer to have robust study data to support their clinical decision making.

There is also a need to better identify, understand, and reduce the risk for comorbidities that appear to be associated with AD.

Recent research into biomarkers has helped us better understand the pathogenesis of atopic dermatitis. Atopic dermatitis is a complex disorder that involves changes in immune factors and the epidermal barrier.[1] Environmental triggers also play a role. Although there is a vigorous controversy about whether AD begins from the "inside out" (primary immune system abnormalities) or the "outside in" (primary barrier defects), it is clear that there is an interplay between the impaired barrier and skewed immune activation. The barrier dysfunction involves deficiency of several proteins in the stratum corneum, stratum granulosum (including filaggrin), and tight junctions, and lipid abnormalities (especially of ceramides and long-chain fatty acids). Abnormalities of the immune system include a decrease in the production of anti-microbial peptides; disruptions involving a wide variety of immune cells, including dendritic cells; and T helper cell abnormalities leading to a marked increase in Th2 and Th22 cells. A cyclic process of exacerbation develops, as the products of these immune disruptions, particulary cytokines IL-4, IL-13, and IL-22, impair expression of barrier proteins and lipids.

Virtually our entire understanding of AD pathogenesis is based on study in adults. Clinicians and researchers increasingly have questioned the relevance of these studies to our approach to AD in children ages two and under, especially given that the clinical manifestations of AD in children two and under can be quite different from those in adults.[2]

Newer studies have demonstrated that lesional skin from children under age five, with their onset of AD within the previous six months, has epidermal thickening similar to rates of epidermal thickening seen in adults with AD or psoriasis. In fact, epidermal keratinocyte proliferation rates are even greater in children with AD than in adults with AD.[2] Despite high rates of transepidermal water loss, signifying barrier impairment, filaggrin levels in biopsied lesional skin of children with early AD are normal in both gene and protein expression, in contast to the

well-recognized and often dramatic reduction in filaggrin expression in adults with AD.[1]

We hypothesize that this filaggrin deficiency in adults results from chronic exposure to Th2 and Th22 cytokines, as well as to *Staphylococcus aureus*. As such, therapies targeting filaggrin expression may not be as useful in children with early AD as in adults. This illustrates the complex role of filaggrin in AD pathogenesis and the need to evaluate the role of other epidermal proteins (beyond filaggrin) and lipids that comprise the normal barrier.

Immune activation, particularly the increased Th2/Th22 expression, seen in the skin of young children with AD is similar to that seen in adults with the disorder, but Th1 expression is quite low. Th1 expression is also very low in the CD4+ CLA+ (skin homing) cells in the the blood of children with AD compared to controls, and leads to a very low Th1/Th2 ratio compared to age-matched controls.[3]

Expression of IL-31, a cytokine mediator for itch produced largely by Th2 cells, is higher in children with AD, compared to similar age-matched controls and higher than rates seen in adults with AD. It activates IL31R/OSMR on keratinocytes and nerves and also signals through JAKs to mediate itch.[2] A better understanding of the pathogenesis of AD from these biomarker analyses may help clinicians to better classify children with AD, with implications for prognosis and treatment. ■

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MORE FROM THE SYMPOSIUM

Atopic Dermatitis Prevention

As understanding of the pathogenesis of AD expands, the next logical question is whether the disease can be prevented. While topical moisturizers are a mainstay of secondary prevention, their possible role in primary prevention has only recently been explored. Eric Simpson, MD reviewed the science behind primary prevention strategies, touching on allergen avoidance, immune modulation, and skin barrier support.

Allergen Avoidance. In terms of allergen avoidance, Dr. Simpson highlighted that guidelines do not support restricting a mother's diet in lactation or pregnancy. More controversial is the role of hydrolyzed infant formulas, which have been recommended to reduce various forms of atopy. A meta-analysis by Boyle, et al. found no statistically significant protection against AD associated with either partially or extensively hydrolyzed formulas. There was no significant difference for casein versus whey.[1] Dr. Simpson and colleagues conducted a meta-analysis looking at dust mite prevention studies, finding that the approach did not offer statistically significant benefit in preventing the development of AD.[2]

Immune modulation. In terms of immune modulation, probiotic supplementation appears to be protective when the body of research is reviewed. There may be approximately a 30 percent reduction in atopic dermatitis associated with probiotic use. However, many different probiotics were used in various different studies and at different doses.[3] "In a high risk population, *Lactobacillus rhamnosus GG* would be the most appropriate during the last four weeks of pregnancy and the first six months of breastfeeding, with the same dose to the infant during the first two years of the child's life," Dr. Simpson said.

Skin Barrier Support. Finally, efforts to enhance the epidermal barrier have been tried in efforts to prevent the initiation of inflammation in the skin and possibly prevent the atopic cycle from starting, especially for infants with a family history of atopy. Dr. Simpson and colleagues showed that it was possible to design and conduct a controlled trial of moisturization versus non-moisturization for the primary prevention of AD.[4] The initial feasibility pilot study for the Barrier Enhancement for Eczema Prevention Study (The BEEP Study has completed enrollment and is ongoing) was not powered for statistical significance. However, the team found a marked reduction in rates of AD at six months among children who had emollients applied to the body daily, compared to those who did not moisturize (43 percent versus 22 percent, respectively). Offered emollients included sunflower oil, an OTC moisturizing cream, and/or a petrolatum-based ointment. Daily moisturizer application to the whole body was found to be safe and acceptable to patients/families. A similar Japanese study assessing the benefit of daily moisturizer application had comparable positive findings (32 percent fewer neonates using moisturizer developed AD/eczema at 32 weeks, relative to controls).[5]

A sub-analysis of swabs taken from various sites on the bodies of moisturizer-applying babies in the BEEP pilot suggests that the cumulative reduction in AD for the moisturizer group may be associated with an observed increased diversity of the microbiome, compared to controls.

Dr. Simpson discussed unpublished data from a controlled study of high-risk infants, which indicates that use of the Mustela Stelatopia line of products may be associated with a prevention of first flare of AD. Parents of children in the

RESEARCH IN FOCUS

What Can We Learn from Modeling Pediatric AD?

Matthias Schmuth, MD, Professor and Chair, Department of Dermatology, Medical University Innsbruck, Austria, offered an update on modeling of pediatric AD and implications for future research and treatment.

The complex pathogenesis of AD makes it a challenge to model the disorder. Among the various factors that interplay to produce the disorder are a genetic predisposition, immune phenomena, and the function—or dysfunction—of the epithelial barrier.[10,11]

Filaggrin deficiency is a pathogenic factor that increases the risk of developing atopic dermatitis. Studies in mouse models with filaggrin deficiency have shown that exposure to allergens can instigate strong Th2-driven inflammation and atopy, not just in the skin but also in the lung (asthma) and the gastrointestinal tract (food allergy), making this a useful research model. However, filaggrin deficiency alone is insufficient for the study of AD, either in the mouse model or in the two-thirds of individuals with ichthyosis vulgaris who do not develop atopic dermatitis.[12]

Organotypic skin equivalents are another emerging tool for investigation of AD. These skin equivalents can be generated using patient cells with defined mutations or using wild-type keratinocytes with gene knockdown of specific genes to evaluate gene function or mimic one or more gene alterations in humans. In addition, introduction of Th2 cytokines into organotypic skin equivalents is able to induce AD-like inflammation, as has been shown with keratinocytes from six-month-old infants. Dr. Schmuth demonstrated research using this model in which topical application of a moisturizing cream (Mustela's Stelatopia balm) led to reduction in chemokines (CCL3, 5, 7), proteases (kallikrein-5), and Th2-induced inflammation.

Organotypic skin equivalents can also be used as a substrate to generate a *Staphylococcus aureus* (*S. aureus*) biofilm, which is recognized to be a frequent aggravating factor of AD lesions. As noted by Dr. Schmuth, pre-treatment of skin equivalents with Stelatopia balm inhibited the adhesion of *S. aureus* and prevented biofilm formation.

active group were instructed to apply emollient balm twice daily to the child, use the cleansing cream twice per week, and use bath oil twice a week. The products contain petrolatum, glycerin, ceramide NP, and sunflower oleosdistillate. Controls applied a glycerin and liquid paraffin-based moisturizer as needed on dry skin. At six months of age, 18 percent of controls developed eczema, whereas 8.3 percent of those using the emollient routine did. These results are in the same range as those from the BEEP pilot study.

A poster presented at the WCPD (Lowe, et al.) showed that daily use of a barrier repair emollient is associated with a reduced cumulative incidence of AD at 12 months compared to controls.

Treatment of AD: A Look at Guidelines

Although clinicians rely on guidelines of care to direct patient management, the current guidelines in atopic dermatitis lack specific recommendations for children aged two and younger. The American Academy of Dermatology and American Academy of Allergy, Asthma, and Immunology/American College of Allergy, Asthma, and Immunology (AAAI/ACAAI) guidelines offer few specific recommendations on medical management of these children, perhaps due to a paucity of published efficacy and safety data in children so young. Lawrence Eichenfield, MD reviewed the available guidelines, noting that they emphasize three components of care: bathing practices and moisturizers, avoidance of irritants and triggers, and treatment of flares.

Skin care and bathing. US guidelines recommend bathing with warm water, followed by topical application of drugs or moisturizers. The AAD actually recommends against additives (except for bleach), which differs from other parts of the world. The AAD Guideline does not delineate a bathing time or bathing frequency.

Moisturizers are indicated as primary therapy, and guidelines consistently acknowledge that hydrophilic ointments offer an advantage. There are large sets of well-designed studies to support various non-prescriptive moisturizing products now on the market; clinicians can be confident recommending skincare to patients, despite a paucity of data comparing various formulations.

Allergen Avoidance. One of the latest developments pertinent to dermatology practice is an addendum to the Guidelines for the Prevention of Peanut Allergy in the United States, which now recommends that infants with severe eczema, egg allergy, or both have introduction of age-appropriate peanut-containing food as early as four to six months of age to reduce the risk of peanut allergy.[6]

Treatment. Treatment of inflammatory dermatitis is warranted in children with AD, with the bulk of experience and data focused on topical corticosteroids (TCS). "Topical corticosteroids are indicated when non-pharmacologic interventions have failed. We know they're effective for inflammation and flare prevention," Dr. Eichenfield explained. Low potency TCS are recommended for maintenance, with higher potency TCS used for flares. There are no specific guidelines on use of TCS in those under age two.

RESEARCH IN FOCUS

What Do We Know About the "Atopic March"?

Christine Bodemer, MD, President of the Genodermatoses and Rare Skin Disorders Network Scientific Committee, spoke about the latest discoveries associated with epicutaneous sensitization and the "atopic march."

A question facing researchers and clinicians is the nature of the relationship between food allergy and AD. One meta-analysis suggested that early life sensitization was significantly related to an increased risk of wheeze, asthma, eczema, allergic rhinitis, eczema in latent fashion with asthma, eczema or allergic rhinitis in childhood, and asthma in young adults.[13]

There is a robust body of rigorous research on the relationship of food allergy to AD. Consensus has emerged that there is a strong dose-dependent association between atopic dermatitis, food sensitization, and food allergies. Filaggrin gene defects are independent predictors of an individual's risk of developing atopic dermatitis, as well as asthma and allergic rhinitis. However, there is no association between filaggrin variance and sensitization, as measured by IgE.[14] The strong and dose-dependent association between AD, food sensitization, and food allergy has been described in a recent systematic review.[15] In most cases, atopic dermatitis symptoms precede food sensitization.

There is also emerging evidence of mental health comorbidities, particularly attention deficit hyperactivity disorder, anxiety, and autism spectrum disorders with AD, as well as with asthma and food allergies. IL-17A cytokine has been shown to be increased in the brain of children with autism or ADHD, suggesting a possible link with atopy.[16]

The issue of corticosteroid labeling may complicate decision-making. Some drugs are indicated for once-daily application, while others are twice-daily. Dr. Eichenfield noted that in clinical practice, once-a-day corticosteroid appears sufficient for many AD patients. Those TCS labeled for use in children under two have data from well-designed trials that monitored HPA axis suppression and found little to no risk. Some TCS have been denied labeling for children two and under because of higher observed rates of adrenal axis suppression.

Standard guidelines recommend use of topical therapies as "proactive maintenance" for children with AD, usually with once- or twice-a-week application of a corticosteroid or topical calcineurin inhibitors (TCIs). "We actually pulled Dr. Jon Hanifin's paper, which was the classic intermittent fluticasone study, and found that they included kids under two (15 percent of the total pool of treated patients)," Dr. Eichenfield explained. Pediatric subjects in the study who applied fluticasone twice-a-week had 8.1-times less chance of developing a flare, as compared to subjects using vehicle.[7]

Steroid phobia is a phenomenon that prescribers must deal with, despite the fact that topical corticosteroids tend to be safe when properly administered. Up to one-third of individuals are not compliant with topical corticosteroid therapy, due to steroid phobia.

Although regulators have suggested that use of TCIs in children under two is concerning, guidelines are liberal regarding such use. There is a significant difference in the data for pimecrolimus versus tacrolimus, with the former having a robust number of children under two studied and providing PK data.[8,9]

Therapeutic developments include the approval of the PDE4 inhibitor crisaborole for the management of AD, although there are no published data regarding use in individuals age two or younger. ■

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