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The ABC's of managing patients with severe atopic dermatitis

Mark Boguniewicz, MD and **Donald Y. M. Leung, MD, PhD**
Division of Allergy-Immunology, Department of Pediatrics, National Jewish Health and University of Colorado School of Medicine Denver, Colo

CLINICAL VIGNETTE

A 3-year-old boy presents with a history of difficult-to-treat atopic dermatitis (AD). He has had an eczematous rash "since birth." The rash initially involved his cheeks and the extensor aspects of the extremities, but more recently, it has also involved the antecubitals, wrists, fingers, lower posterior trunk, popliteals, and ankles. He has had increased itching and has not been sleeping well. In the past, the eczema had responded to topical corticosteroids. He has also been treated with a moisturizing lotion and cetirizine once daily. More recently, he was treated with oral antibiotics twice for suspected skin infections. His parents are concerned that food allergy might be the cause of the child's AD. Recently, his pediatrician measured his serum IgE level, which was 3176 IU/mL, and also sent off sIgE measurements to a panel of common food allergens. The parents state that these were "all positive." The parents have struggled to eliminate all of the foods reported as positive, but the child's AD continues to flare.

The patient has wheezed with several viral upper respiratory tract infections and, more recently, when he slept over at a friend's home, where a cat was present. There are no furred animals in the home, and the child is not in day care. His mother has a history of childhood asthma, and his older brother has hay fever.

On examination, the patient was uncomfortable and scratched continuously when undressed. He had excoriated, lichenified eczematous lesions involving his lower back, antecubitals, wrists, popliteals, posterior thighs, and ankles. He had scaling of the anterior distal lower

Corresponding author: Donald Y. M. Leung, MD, PhD, National Jewish Health, 1400 Jackson St, Rm K926i, Denver, CO 80206. leungd@njhealth.org..

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Activity Objectives

1. To discuss recent insights into skin barrier and immune abnormalities in patients with atopic dermatitis.
2. To recognize the reasons for treatment failure in patients with severe atopic dermatitis.
3. To educate patients and caregivers regarding the basics of skin care for atopic dermatitis.

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extremities and hyperlinear palms. He had no pustular or vesicular lesions, although multiple individual punched-out crusted papules were noted on his face (see Fig E1 in this article's Online Repository at www.jacionline.org). His hair and nails were normal. He had shotty, nontender cervical and inguinal nodes bilaterally. The remainder of his examination was unremarkable.

Because of poorly controlled AD not responding to outpatient therapy and complicated by cutaneous infection, this child was admitted to our multidisciplinary eczema day unit (described in Boguniewicz et al[E1]). Swabs of excoriated lesions were sent for culture and sensitivity, and PCR testing was performed on punched-out lesions. While awaiting results, the patient was started on oral acyclovir. Skin cultures showed a few areas of methicillin-sensitive *Staphylococcus aureus*, and PCR was positive for herpes simplex virus (HSV). He was started on a nurse-supervised skin care regimen with soaking baths in warm water for 10 minutes twice daily with the assistance of a child life therapist to distract him. A midpotency topical steroid ointment was applied to eczema lesions on the trunk and the extremities twice daily, and moisturizing cream was applied to clear areas. A sedating medication was added at bedtime. Wet wraps were applied to the most severe eczema of the extremities at bedtime for 4 days and then discontinued. Behavioral modification for itch control was instituted by a pediatric psychologist, and parents received hands-on education from the nursing staff. The patient had significant clearing of skin lesions and a dramatic decrease in pruritus and scratching. The parents were provided with a written stepped-care plan for home management.

The full version of this article, including a review of relevant issues to be considered, can be found online at www.jacionline.org. If you wish to receive CME or MOC credit for the article, please see the instructions above.

REVIEW

High prevalence rates of AD have been observed in a number of countries, with data from more than a million children in 97 countries showing that AD is a major problem in developing, as well as developed, countries.[E1,E2] Pruritus is a key symptom and, together with sleep disturbance, significantly affects the quality of life of patients and their families.

Skin barrier and immune abnormalities

A number of investigations into the pathogenesis of AD have pointed to both immune dysregulation and epidermal barrier abnormalities.[E3] The complexity of the skin barrier was recently reviewed with a physical barrier, including the stratum corneum and tight junctions; a microbiome barrier of colonizing organisms; a chemical barrier of antimicrobial peptides; and an immunologic barrier.[E4] Mutations in the gene encoding the epidermal barrier protein filaggrin *(FLG)* have been shown to be strongly associated with the risk for AD.[E5] Not only is filaggrin a major structural component of the stratum corneum, but also amino acids from filaggrin breakdown products contribute to skin hydration and affect skin pH. In turn, the latter can influence the activity of endogenous and exogenous proteases, as well as microbial colonization.[E6] Importantly, patients with *FLG* mutations have been shown to have earlier onset and more severe and persistent AD and are more likely to wheeze and have allergic sensitization. Also, they have been shown to have an increased risk for eczema herpeticum.

Although *FLG* mutations are the most important risk factor for AD and occur in approximately 50% of patients with severe AD,[E6] not all patients with AD have *FLG* mutations, and even those with mutations can go into remission. Indeed, the majority of patients with AD will have filaggrin deficiency caused by cytokine dysregulation. In fact, filaggrin expression has been shown to be downregulated by T_H2 and T_H22 cytokines.[E6]

Susceptibility of patients with AD to microbial infection or colonization

Patients with AD have an increased susceptibility to infection or colonization with a variety of organisms. These include infections with HSV and *S aureus*. Of note, patients with AD in whom eczema herpeticum develops (ADEH) have more severe T_H2-polarized disease with greater allergen sensitization. They are also much more likely to experience cutaneous infections with *S aureus*. Patients with ADEH have also been shown to have reduced IFN-γ production, and *IFNGR1* variants are significantly associated with ADEH.[E7]

Therapeutic implications of research insights

Key observations with important therapeutic implications are that normal-appearing skin of patients with AD contains infiltrating lymphocytes and that these patients manifest skin barrier abnormalities in nonlesional skin.[E8] These observations provide the rationale for maintenance or proactive therapy in patients with AD. Of note, increased binding of *S aureus* to AD skin is related to underlying skin inflammation, and anti-inflammatory treatment with both topical steroids and calcineurin inhibitors reduces *S aureus* colonization.[E9] In patients with a relapsing course, after a period of stabilization, proactive therapy with either a topical steroid or calcineurin inhibitor improves disease control and reduces the number of flares.[E10]

More recent insights into the pathophysiology of AD with therapeutic implications include those addressing mechanisms of disease onset and persistence. Gittler et al[E11] investigated intra-personal sets of transcriptomes from nonlesional skin and acute and chronic lesions of patients with AD through genomic, molecular, and cellular profiling. Onset of acute lesions was associated with an increase in a subset of terminal differentiation proteins and significant increases in gene expression levels of T_H22 and T_H2 cytokines. Further significant intensification of T_H22 and T_H2 cytokines was observed between acute and chronic lesions. In addition, AD lesions tend to recur in the same locations after treatment, suggesting that residual cellular and molecular alterations might predispose to new lesions.[E12] These findings will need to be addressed as novel targeted and pharmacogenomics-based therapies are developed for AD.

Fundamentals of therapy in patients with severe AD

In approaching the management of patients with severe AD, clinicians need to review the fundamentals of therapy before considering the patient a treatment failure and prescribing systemic immunosuppressive treatments.[E13] This includes assessment of irritants, allergens, infectious agents, and emotional stressors. Negative skin test results with proper controls have a high predictive value for ruling out suspected allergens, whereas positive skin test results have a lower correlation with clinical symptoms in patients with suspected food allergen–induced AD.[E14] Specific IgE to food allergens measured by using the ImmunoCAP assay (Phadia, Uppsala, Sweden) can be helpful in determining the probability of a clinical reaction for a limited number of foods, although the levels do not identify the type or severity of reaction. Extensive elimination diets are almost never warranted. In a study of children predominantly with AD evaluated for food allergy, 89% of oral food challenge results were found to be negative.[E15] In this cohort milk, egg, peanut, soy, wheat, tree nuts, and shellfish accounted for the majority of clinically relevant food allergies. The 95% predictive decision points for food-specific IgE were useful for milk, egg, and peanut.

Because patients with AD have increased transepidermal water loss, reduced water-binding capacity, and decreased ceramide levels in their skin, hydration through soaking in warm water for approximately 10 minutes combined with an occlusive agent to retain the absorbed water is an essential component of therapy. Bathing also removes allergens and reduces colonization by *S aureus*.

The practice parameter update reaffirmed the fundamental anti-inflammatory and antipruritic role of topical steroids in patients with AD, with higher-potency steroids reserved for acute exacerbations of AD.[E13] Of note, patients or caregivers often delay treatment with these medications during flares of AD. Thus clinicians should use a "what, when, and where" approach to reviewing skin care. Inadequate prescription size is another contributing factor for suboptimally controlled AD.[E1] Written instructions using a stepped-care approach are critical to improving outcomes (an example of such a plan is provided in Boguniewicz et al[E1]). Of note, a limited number of topical steroids are approved for children less than 2 years of age, and even those are labeled for use up to 4 weeks. For the most part, systemic steroids, including oral prednisone, should be avoided in the management of a chronic relapsing disorder, such as AD. Although patients or caregivers often demand immediate relief and find systemic steroids more convenient to use than topical therapy, the dramatic improvement observed with their use is often followed by an equally dramatic flaring of AD after discontinuation, leading to a vicious cycle or erythrodermic rebound.

Topical calcineurin inhibitors (TCIs) as nonsteroidal agents for the treatment of AD have proved effective with a good safety profile, even with long-term administration. Because use of TCIs is not associated with skin atrophy, they are particularly useful for treatment of eczema involving the face, axillae, or groin or on skin with atrophic changes. Ongoing surveillance has not shown a trend for increased frequency of infections or problems with response to childhood vaccinations. Currently, tacrolimus ointment 0.03% is approved for intermittent treatment of children aged 2 years and older with moderate-to-severe AD, tacrolimus ointment 0.1% is approved for intermittent treatment of adults with moderate-to-severe AD, and pimecrolimus cream 1% is approved for intermittent treatment of patients aged 2 years and older with mild-to-moderate AD. Although there is no evidence of a causal link of cancer and the use of TCIs, the US Food and Drug Administration has issued a "boxed" warning for TCIs because of a lack of long-term safety data. The labeling states that these drugs are recommended as second-line treatments and that their use in children less than 2 years of age is currently not recommended. Proactive therapy with tacrolimus ointment in both adults and children with AD, similarly to topical steroids, has been shown to be more effective than a reactive approach.[E10] Although this would be considered off-label therapy in the United States, in Europe proactive therapy with tacrolimus ointment has been approved for use in children 2 years or older with AD for up to 12 months.

Addressing the itch-scratch cycle in patients with AD is a key part of successful management because pruritus is typically the least tolerated symptom of AD. The cause of pruritus in patients with AD is complex, with a number of mediators other than histamine, including neuropeptides and cytokines, involved. Systemic antihistamines and anxiolytics remain useful for many patients through their tranquilizing and sedative effects and should be used primarily at bedtime. If nocturnal pruritus remains severe, short-term use of a sedative to allow adequate rest might be appropriate. Behavioral modification and biofeedback therapy have also been useful as adjunctive therapy.

Although patients with AD are typically colonized by *S aureus* and often secondarily infected, a number of therapies directed at healing the skin barrier, including hydration and use of anti-inflammatory therapies, can reduce bacterial load. Systemic antibiotic therapy might be necessary to treat overt infections. Antibiotic sensitivities from culture should be obtained to direct therapy, especially with the increase in colonization or infection by methicillin-resistant *S aureus*.[E16] Bleach baths with dilute sodium hypochlorite (¼-½ cup of household bleach per full tub of water) can be considered for patients with recurrent skin infections, especially with methicillin-resistant *S aureus*, but might cause skin irritation, with pruritus and scratching leading to further skin barrier damage.[E13] Rinsing off afterward might remove irritating chemical residue from the skin.

HSV infection is often missed in patients with AD, especially if lesions become impetiginized. HSV can be diagnosed either by doing a Tzanck smear of cells scraped from the base of a freshly unroofed vesicle, viral PCR, or culture. Patients with disseminated HSV (ADEH) require treatment with systemic acyclovir or related antiviral agents, and if they appear toxic, they should be hospitalized with intravenous therapy. Periocular lesions should be evaluated by an ophthalmologist. Daily prophylactic oral acyclovir can be considered in patients with AD with recurrent HSV infections.

In patients with severe recalcitrant AD, selective use of wet-wrap therapy in conjunction with skin hydration and topical steroids can break their vicious cycle of itch-scratch-relapse (see Boguniewicz et al[E1]). Wet-wrap dressings reduce pruritus and inflammation, act as a barrier to trauma associated with scratching, and improve penetration of topical steroids. In addition, wet-wrap therapy has been shown to improve epidermal barrier recovery, which persists even after wrap therapy is discontinued.[E17] Wet-wrap therapy should be reserved for difficult to manage AD and should not be overused because it can result in secondary infection. Of note, the package inserts for TCIs recommend that they should not be used under any occlusive dressing.

New directions in therapy

Patients with AD have a relative defect in innate immunity because they express lower levels of antimicrobial peptides, such as human β-defensins 2 and 3 and cathelicidin LL-37, in inflamed skin. The observation that cathelicidin expression in human subjects is induced by 1,25-dihydroxyvitamin D3 points to just one aspect of a complex interaction of this vitamin with a number of immune cells (as reviewed by Muehleisen and Gallo[E18]) and suggests a role for vitamin D3 therapy in patients with AD. The current practice parameter states that patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level of vitamin D.[E13]

Because T_H2 cytokines have been shown to inhibit filaggrin expression and antimicrobial peptide responses, cytokine-modulating therapies could ameliorate barrier abnormalities. In this respect both topical steroids and TCIs (as discussed above) have been shown to reverse reduced filaggrin expression in patients with lesional AD. Targeted immunomodulatory therapy, including IL-4 receptor antibody or anti–thymic stromal lymphopoietin, offers potential advances in therapeutics for subsets of patients with AD.[E5,E11,E13] In addition, gene expression and immunohisto-chemistry studies of lesional and nonlesional skin in patients with moderate-to-severe chronic AD treated with narrow-band UVB phototherapy showed that epidermal hyperplasia and differentiation normalized with suppression of T_H2 and T_H22 immune pathways.[E19]

THE CASE REVISITED

This child with AD complicated by HSV infection illustrates a number of problems encountered by clinicians dealing with this common, chronic, relapsing disease. This child's pruritic eczematous rash with flexural distribution and a relapsing course, along with a personal and positive family history of atopy and increased serum IgE levels, fulfills both the major and minor criteria of Hanifin and Rajka for the diagnosis of AD. However, as shown in the flowchart of the diagnosis and management of AD in the current practice parameter,[E13] clinicians should consider other conditions in patients not responding to the usual therapies. This patient's history of onset in infancy with a persistent severe course, atopic sensitization, and recurrent respiratory symptoms suggestive of asthma is strongly suggestive of an AD phenotype with associated *FLG* loss-of-function mutation, and the physical findings of skin scaling and palmar hyperlinearity further support this association.[E6] The punched-out appearance of the patient's lesions, even without blistering,

should raise suspicion for HSV. It is important that clinicians consider immunodeficiency with mutations in dedicator of cytokinesis 8 in the differential diagnosis in their evaluation of a patient with severe AD complicated by HSV infections.[E20]

Although there are currently no specific treatments for correcting filaggrin deficiency, basic skin care measures using an ABC approach of *avoidance* of triggers, *barrier* repair and maintenance, and *control* of inflammation and infection (Table E1) are essential. Education is a key component of a successful treatment plan because patients and caregivers often have a poor understanding of the chronic relapsing nature of the disease and triggers, as well as having concerns about prescribed medications.[E1] Although patients and caregivers might provide a history suggesting adherence to a prescribed treatment plan, closer review or direct observation frequently reveals incorrect or inadequate implementation of the recommendations. Under supervision, this child was able to improve his skin hydration regimen significantly, which, together with appropriate use of moisturizers, topical anti-inflammatory therapy, a short course of wet wraps, and antiviral therapy, led to dramatic clinical improvement in a short period of time. With clearing of his eczema and resolution of HSV infection, this patient was able to transition to a twice-weekly regimen with fluticasone 0.05% cream to previously involved areas of recurring eczema. Additionally, clearing of eczema allowed for select allergy skin prick testing after the patient was able to hold oral antihistamine for 4 days. This patient was tested only to the 5 most common food allergens that he ate on a regular basis (milk, egg, peanut, wheat, and soy), with egg eliciting the only positive result. The parents elected to eliminate all egg from the patient's diet for 3 to 4 weeks while restarting the foods eliciting negative skin test results individually, one per week. In addition, the parents reintroduced foods with positive results on *in vitro* testing but with poor clinical correlation, without any signs or symptoms noted (eg, orange, tomato, and corn).

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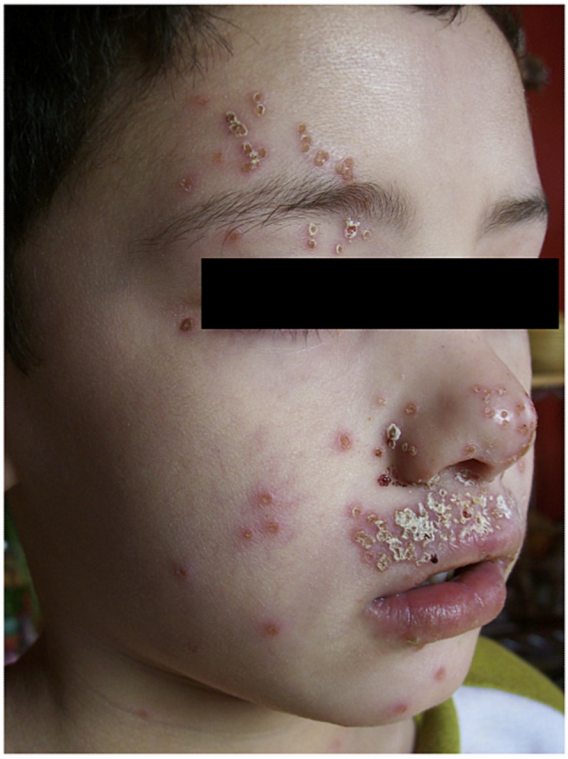

FIG E1.
Child with ADEH.

TABLE E1

ABC's of atopic dermatitis

A = Avoidance of triggers (eg, irritants and proved allergens)
• Educate patients and caregivers about role of irritants
• Approach allergy evaluation in a critical manner, informing patient/caregiver before testing about predictive values of positive and negative test results, pros/cons of dietary eliminations, risks vs benefits of food challenges, and environmental control measures
B = Barrier repair and maintenance
• Emphasis on hydration and moisturizers
• Address itch-scratch cycle with medications but also behavioral modification
• Consider wet-wrap therapy for limited periods of time to areas of recalcitrant AD
C = Control of inflammation and infections
• Consider proactive (twice weekly) therapy in patients with relapsing course
• Use diagnostics effectively (eg, culture and sensitivity test, viral culture, or PCR)
• Use antimicrobial agents appropriately
• Use topical corticosteroids and TCIs appropriately (eg, prescribe appropriate potency, vehicle, and quantity)