Clinical pearls

Atopic dermatitis

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Atopic dermatitis (AD) is a common chronic inflammatory skin disease that often presents with flares and can be complicated by recurrent skin infections.[1] Given the increase in prevalence that approaches 17% in school-aged children in the United States, clinicians are frequently faced with a number of diagnostic and therapeutic decisions in managing these patients. This review addresses some of the questions raised by clinicians and discusses practical aspects of dealing with this distressing dermatitis.

Abbreviations used
AD: Atopic dermatitis
APT: Atopy patch test
HSV: Herpes simplex virus
SIT: Specific immunotherapy
SPT: Skin prick test

WHAT SHOULD THE APPROACH BE TO THE PATIENT WITH AD AND RECURRENT SKIN INFECTIONS?

A normal skin barrier plays a critical role in providing first-line defense against microbial attack. The basics of skin care include hydration, use of emollients, and avoidance of irritants and proved allergens and have been discussed in various reviews.[2] Bacterial infections are predominantly caused by *Staphylococcus aureus*, the majority of which secretes toxins with superantigenic properties. Toxins bind avidly to the skin and interact not only with a high number of T cells but also other resident or skin-infiltrating cells, with subsequent release of multiple proinflammatory cytokines leading to erythroderma and other acute inflammatory responses in the skin. Severity of disease correlates better with toxin-specific IgE levels, rather than total serum IgE levels.

Although short courses of systemic antistaphylococcal antibiotics and even topical therapy for localized, milder impetiginized eczema is appropriate, it is critical not to start patients on prolonged antimicrobial therapy because they can become colonized with resistant organisms. Baths and gentle cleansers reduce *S aureus* colonization, and antibacterial cleansers such as Lever 2000 (Unilever, Englewood Cliffs, NJ), can reduce them even further, as long as the patient is able to tolerate such products. Most patients with AD do not tolerate harsher antibacterial products, such as chlorhexidine or other antiseptics or bleach baths, although it is reasonable to consider these approaches in the patient prone to bacterial skin infections. The nose has been shown to be the major reservoir of *S aureus*. Intranasal mupirocin applied twice daily for 5 to 7 days can eradicate *S aureus* and improve eczema. Of note, topical immunomodulators, whether steroids or calcineurin inhibitors, have been shown to reduce *S aureus* colonization. Importantly, an increase in methicillin-resistant *S aureus* is being reported. Despite this, most patients with AD and methicillin-resistant *S aureus* do not appear toxic and do not require parenteral antibiotic therapy, suggesting that repair of the epidermal barrier and topical anti-inflammatory medications are critical components of successful therapy.

It is important to recognize that AD skin can be infected with herpes simplex virus (HSV). This can be mistaken for impetigo because such lesions can be superinfected with *S aureus*, and clinicians need to recognize the punched-out individual lesions with an erythematous base, even if vesicles are not present. Ideally, viral PCR, Tczank preps, or culture should be obtained by unroofing an intact vesicle because positive yield from excoriated lesions is low. Patients usually respond well to oral antiviral therapy

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with acyclovir or valcyclovir, although some patients with recurrent breakouts might require prophylactic therapy. Clinicians often discontinue treatment of AD lesions in the face of active HSV infection. In fact, once a patient is started on appropriate antiviral therapy, treatment of eczematous rash with topical immunomodulators should be continued to allow appropriate healing of the skin barrier. Disseminated infection with HSV (eczema herpeticum or Kaposi's varicelliform eruption) represents a severe and potentially life-threatening complication requiring systemic antiviral treatment.

WHAT IS THE ROLE OF FUNGI, SUCH AS *MALASSEZIA* SPECIES, IN AD?

The presence of specific serum IgE, positive skin prick test (SPT) and atopy patch test (APT) results, or both against *Malassezia* species have been demonstrated in patients with AD. Sensitization rates in Europe vary from 30% to 68% in adult patients on the basis of *Malassezia*-specific serum IgE levels. A recent study from the United States done in a dermatology clinic found that the subgroup of adult patients with head, neck, and upper torso distribution of AD were more likely to react on APTs to *Malassezia sympodialis*.[3] *Malassezia* species–specific IgE has also been reported in the subgroup of patients with AD with intrinsic type of AD.

Diagnosis of *Malassezia* species sensitization can be made by means of specific serum IgE measurement or skin tests. Serum IgE against *M sympodialis* extract can be measured by using the ImmunoCAP assay. Recently, a new assay measuring IgE to several species of *Malassezia* has been introduced (m227), leading to a slightly increased sensitivity. Skin test extracts with *Malassezia* species are not yet commercially available. The use of single recombinant allergens might improve the specificity of the diagnosis of *Malassezia* species sensitization.[4]

Antifungal therapy has been shown to be effective in a subgroup of patients with AD in several studies, with most studies showing a correlation between response to antifungals and levels of fungal-specific IgE. The combination of itraconazole, 100 mg/d, for 1 week followed by 200 mg/d weekly seems to be the minimal effective dose. However, the mechanism of antifungal therapy in AD remains to be clarified. Ketoconazole or itraconazole both inhibit IL-4 and IL-5 production and ergosterol synthesis, which might lead to nonspecific anti-inflammatory effects and also reduced *Malassezia* species–specific IgE and total IgE levels. Thus the anti-inflammatory effect of antifungals might be as important as the fungicidal activity.

WHAT ROLE DO ANTIHISTAMINES PLAY IN THE MANAGEMENT OF AD?

Pruritus is the most common and least tolerated symptom of AD, and even partial reduction of pruritus can result in significant improvement in quality of life for patients. However, the role of histamine in pruritus caused by AD has been questioned, and mediators, such as neuropeptides and cytokines, might be important as centrally acting agents, such as opioid receptor antagonists, which have been shown to be effective in the itch of AD. In this respect treatment with systemic or topical steroids and calcineurin inhibitors, which results in decreased transcription of a number of proinflammatory cytokines, leads to rapid improvement in pruritus in patients with AD. First-generation antihistamines might be of value primarily for their soporific effects when given at bedtime. On the other hand, second-generation antihistamines have been found to be ineffective in treating the pruritus associated with AD, except in that subset of patients with chronic urticaria or rhinitis. In a study looking at the potential role of a second-generation antihistamine in preventing progression of atopic disease, treatment of a large cohort of young children with AD with cetirizine for 18 months did not show a statistical difference between the cetirizine group versus the placebo group in reducing the number who had asthma, although analysis of those subgroups sensitized to house dust mite or grass pollen suggested a beneficial effect. However, a subsequent study with levocetirizine in children with AD sensitized to allergens apparently showed no benefit. Treatment of AD with topical antihistamines should be avoided because of potential sensitization.

HOW DO YOU MAKE SENSE OF MULTIPLE POSITIVE SKIN TEST RESPONSES OR IMMUNOCAP ASSAY RESULTS TO FOOD ALLERGENS IN PATIENTS WITH AD?

Patients with AD can have very high serum IgE levels, often more than 10,000 IU/mL. It is important to note that specific IgE against allergens, whether measured *in vivo* by using SPTs or by using *in vitro* assays, does not equate to clinical disease or define clinical relevance in a given patient. In general, properly done SPTs to food allergens have a high negative predictive value, but the positive predictive value is only slightly higher than 50% for all patients on the basis of controlled food challenges done at National Jewish. Patients with multiple positive test results might need to undergo formal food challenges to confirm food allergy. Consultation with a dietitian might be needed because elimination of multiple foods without proper guidance can result in a malnutritious diet. Of note, some patients with AD have been observed to have delayed reactions on food challenge, and in case of a negative immediate challenge result, the patient's skin might need to be examined on the following day. Although positive food challenge results are often stopped after the first clinical sign of a reaction (often a transient rash that might not resemble AD), repeated challenges provoking such a cutaneous reaction (not recommended in the usual clinical setting) could result in the development of eczematous dermatitis after several days. Importantly, avoidance of

the implicated allergen would lead to clinical improvement. Use of the ImmunoCAP assay to define decision points for certain foods was recently reviewed in a ''Clinical pearls'' article, remembering that data curves have been generated for only some, albeit the more common, food allergens.[5] This can be especially helpful in following the natural history of clinically relevant food allergies, comparing values over time, and deciding on when to do a food challenge or reintroduce a food that has been eliminated from the diet. It is crucial to recognize the limitations of this assay, especially that the lower end of the probability curve is not 0 but less than 0.35, and rarely patients can react on food challenge with very low levels of food-specific IgE. The role of the APT in defining clinically relevant food allergy in patients with AD has been reported, but at present, it remains investigational.

WHEN WOULD YOU CHOOSE A TOPICAL CALCINEURIN INHIBITOR RATHER THAN A TOPICAL STEROID, AND DO TOPICAL CALCINEURIN INHIBITORS CAUSE CANCER?

Given the concerns of using topical corticosteroids for a chronic, relapsing inflammatory disease, development of topical nonsteroidal agents has been a welcome addition to the treatment armamentarium for AD. Because topical calcineurin inhibitors do not cause skin atrophy, they are especially useful for treatment of AD involving the face, including periocular and perioral dermatitis. In addition, use in other areas prone to skin atrophy, such as the axillae and groin, would be advantageous. Of note, in a yearlong study, treatment with topical calcineurin inhibitor monotherapy appeared to reverse steroid-induced atrophic changes in patients with AD.[6] Another subgroup of patients who might benefit from treatment with a topical calcineurin inhibitor are those with steroid-insensitive or ''resistant'' AD.[7] Given the important role that *S aureus* toxins play in AD,[2] the observation that calcineurin inhibitors, but not steroids, suppress superantigen-driven immune proliferation might be clinically important.[8]

Several studies with pimecrolimus 1% cream have shown that early intervention at the first sign of redness, induration, or pruritus results in fewer flares of AD and significantly less need for corticosteroid rescue therapy. This approach is currently being evaluated in a long-term intervention study that will look not only at the effect on the natural history of AD but also on the prevention of asthma and allergies.[9] Topical calcineurin inhibitors, including tacrolimus ointment 0.03% and pimecrolimus cream 1%, are currently approved down to 2 years of age in the United States (although pimecrolimus cream 1% is approved for patients younger than 2 years in several countries). Tacrolimus ointment 0.1% is approved for adult patients, although it has been studied and used extensively in children younger than 16 years of age. Because of concerns raised by the US Food and Drug Administration's Pediatric Advisory panel, the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology reviewed all available data and concluded that the risk/benefit ratio of topical pimecrolimus and tacrolimus are similar to those of most conventional therapies for the treatment of chronic relapsing eczema.[10] Furthermore, in children less than 2 years of age with poorly controlled persistent AD who require more than hydration and use of emollients to keep their skin disease under control, use of off-label therapy might be necessary because most topical steroids or other immunomodulators have not been studied or approved in this age group (eg, fluticasone cream 0.05% is approved down to 3 months of age for up to 28 days, and fluticasone lotion was approved recently down to 12 months of age). Despite the task force's conclusions and statements by a number of other medical and lay organizations, the US Food and Drug Administration issued a ''black box'' warning for long-term continuous treatment with both tacrolimus ointment and pimecrolimus cream, while acknowledging that there is no evidence for a causal link of cancer and the use of topical calcineurin inhibitors. Long-term surveillance studies for both drugs are in progress, and it is reassuring that in a recent study a large group of infants 3 to 23 months of age treated intermittently for up to 2 years with pimecrolimus cream 1% demonstrated normal immune responses to vaccinations and did not show any increase in skin infections.[11]

WHAT ABOUT THE PATIENT WITH VERY RECALCITRANT DISEASE?

Most patients with AD will respond to conventional treatment.[12] When a patient presents as a treatment failure, it is worthwhile to confirm compliance with prior conventional treatments before prescribing medications that might have significant side effects. This would include checking whether the patient is avoiding irritants and proved allergens, hydrating the skin properly, addressing the itch-scratch cycle, treating complicating infections, and using topical immunomodulators, whether steroids or calcineurin inhibitors, effectively. Day hospitalization might be a good option for patients with severe AD resistant to conventional therapy. Often, removing the patient from environmental allergens or stressors, together with intense education and assurance of compliance with therapy, results in marked clinical improvement. In addition, topical therapy can be potentiated with wet-wrap therapy. In this setting the patient can also undergo appropriately controlled provocative challenges to help identify potential triggering factors. If, despite this, the patient requires additional therapy, short courses of cyclosporin A might be effective, with data reported in both pediatric and adult populations.[12] Other treatments to consider include phototherapy, mycophenolate mofetil, azathioprine, and intravenous gammaglobulin. However, these should be prescribed by AD experts well versed in use of these therapeutic agents and their potential side effects.

IS THERE A ROLE FOR SPECIFIC IMMUNOTHERAPY OR OMALIZUMAB IN AD?

Although a number of anecdotal and case reports suggest clinical benefit from allergen-specific desensitization (specific immunotherapy [SIT]) in AD, one double-blind controlled trial in children with dust mite allergy and AD failed to show efficacy of SIT compared with placebo after 8 months of therapy.[13] However, treatment for an additional 6 months resulted in clinical improvement, suggesting that prolonged desensitization might be more effective than placebo, but the numbers were too small to permit confident conclusions. A more recent multicenter, randomized, blinded, dose-response trial with house dust mite SIT in 89 adults with chronic AD sensitized to dust mite showed that the SCORAD score decreased in the 3 dose groups in a dose-dependent manner and was significantly lower in the 2 high-dose groups compared with the low-dose group after 1 year of SIT.[14] The use of topical corticosteroids was also significantly reduced with higher doses, suggesting that SIT might be useful for patients with AD sensitized to house dust mite. Children with AD with or without respiratory allergies or asthma have also been treated with allergen-specific oral (swish-swallow method) desensitization, with 69% of the group without respiratory allergies-asthma versus 74% of the group with respiratory allergies-asthma showing complete resolution of their skin disease after 24 months of therapy.[15] This form of SIT was safe and well tolerated by patients. Nevertheless, these results were generated in an open-label study, with a relatively small number of patients studied.

The role of omalizumab in AD remains to be defined. The current anti-IgE antibody might be of limited usefulness, given its limitations in patients with high IgE levels, although it could have a role in patients with AD and concomitant food allergy. A recent case report described success in 3 children ages 10 to 12 years with severe recalcitrant AD who had serum IgE levels ranging from 1990 to 6120 IU/mL.[16] These data clearly need to be confirmed in a controlled study.

FINAL QUESTION: WATER AVOIDANCE OR FREQUENT BATHING?

Although patients continue to receive conflicting information regarding bathing, it is clear that they have an abnormal epidermal barrier with increased transepidermal water loss. Rehydration of the skin is therefore beneficial, whereas evaporation would lead to further skin damage. It is critical, then, to protect the hydrated skin barrier with a layer of emollient or topical medication applied immediately after bathing or showering, while the skin is still damp. Our experience at National Jewish with patients with severe disease suggests that they benefit from several soaking baths each day when their eczema is flaring, and most have their symptoms managed long term with once-daily baths.

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