

Recent insights into atopic dermatitis and implications for management of infectious complications

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Activity Objectives

1. To better understand the various epidermal abnormalities and immune dysregulation in atopic dermatitis (AD).
2. To better understand the immunologic components of the itch-scratch cycle.
3. To better understand the role of microbial organisms in AD severity and associated infections.
4. To better understand the effects of topical therapy on the skin barrier and novel directions for new therapies for AD.

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Atopic dermatitis (AD) is a common complex disease that frequently follows a chronic relapsing course and affects the quality of life of patients and families in a significant manner. New insights into the pathophysiology of AD point to an important role of structural abnormalities in the epidermis combined with immune dysregulation. Patients with AD have a unique predisposition to colonization or infection by a number of microbial organisms, most notably *Staphylococcus aureus* and herpes simplex virus. A multipronged approach directed at healing or protecting the skin barrier and addressing the immune dysregulation is necessary to improve the likelihood of successful outcomes. (*J Allergy Clin Immunol* 2010;125:4-13.)

Key words: *Atopic dermatitis, filaggrin, epidermal barrier, Staphylococcus aureus, herpes simplex virus, superantigens, T regulatory cells, eczema herpeticum, antimicrobial peptides, probiotics*

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Abbreviations used

AD:	Atopic dermatitis
ADVN:	Atopic Dermatitis and Vaccinia Network
<i>agr</i> :	Accessory gene regulator
AIP:	Autoinducing peptide
CA:	Community acquired
CLA:	Cutaneous lymphocyte-associated antigen
EH:	Eczema herpeticum
<i>FLG</i> :	Filaggrin gene
FoxP3:	Forkhead box protein 3
HBD:	Human b-defensin
H4R:	H4 histamine receptor
HSV:	Herpes simplex virus
IVIG:	Intravenous immunoglobulin
LTA:	Lipoteichoic acid
MRSA:	Methicillin-resistant <i>Staphylococcus aureus</i>
SAg:	Superantigen
SEB:	Staphylococcal enterotoxin B
TEWL:	Transepidermal water loss
Treg:	Regulatory T
VV:	Vaccinia virus

Atopic dermatitis (AD), a complex, chronic, relapsing inflammatory skin disorder continues to be an important disease worldwide.^{1,2} Lifetime prevalence in school-aged children in the United States has been reported to be up to 17%.³ Similarly

high prevalence rates have also been observed in a number of other countries.⁴ Most recently, data on eczema symptoms from more than a million children in 97 countries showed that AD is a major problem in developing, as well as developed, countries.⁵ Atopy remains an important association, with an incidence of approximately 80% in infants with AD recently reported in Australia and the United Kingdom.⁶ Importantly, a high percentage of children with AD (approximately 66%) have asthma, allergies, or both, typically by 3 years of age.⁷

Patients with severe or persistent disease and their families experience significant impairment in their quality of life, which can contribute to poor outcomes with prescribed treatment.⁸ In addition, AD places a heavy economic burden not only on patients and their families but also on society as a whole.^{9,10} This review will highlight some of the recent studies that provide insights into the pathophysiology of AD, with emphasis on the unique role that microbial organisms play in this disease and implications for therapy.

EPIDERMAL ABNORMALITIES AND IMMUNE DYSREGULATION IN PATIENTS WITH AD: RECONCILING THE OUTSIDE-IN AND INSIDE-OUT HYPOTHESES

The pathophysiology of AD remains incompletely understood, although gene-environment interactions in genetically predisposed individuals (see the article by Barnes¹¹ in this issue) play a central role.¹² A number of critical systemic and skin immune abnormalities, including increased serum IgE levels and sensitization to allergens, increased T_H2-type cytokine expression in acute lesions, increased numbers of T cells expressing cutaneous lymphocyte-associated antigen (CLA; the homing receptor for the skin), increased expression of FcεRI on both Langerhans cells and inflammatory dendritic epidermal cells, and decreased expression of antimicrobial peptides, have been seen.^{13,14} A growing number of studies have shown a highly significant association between abnormalities in the epidermal barrier and the risk of early-onset, severe, persistent AD.¹⁵⁻¹⁷ Of note, these might be due to both mutations of genes encoding proteins, such as filaggrin,¹⁴ and modulation of epidermal protein levels by T_H2-type cytokines.^{18,19} Although some researchers have argued that the primary defect in AD resides in the epidermal barrier,²⁰ it is important to recognize that a significant number of patients with AD do not have any of the known filaggrin gene (*FLG*) mutations, and conversely, approximately 40% of patients with *FLG*-null alleles do not have AD.²¹ In addition, although the natural history of patients with AD and *FLG* mutations has not been fully elucidated, many of these patients outgrow their disease or experience an extended remission, although they tend to have a more prolonged course than those without *FLG* mutations.²² A critical link between the barrier defect in patients with AD with *FLG* mutations and T_H2 polarization could be explained in part by enhanced allergen penetration through the damaged epidermis accompanied by increased production of thymic stromal lymphopoietin by keratinocytes, leading to a T_H2-type milieu.²³ Importantly, patients with *FLG* mutations are at increased risk for asthma but only in the context of having AD, pointing to the importance of allergic sensitization through a damaged skin barrier.²⁴ Conversely, patients with AD with more polarized T_H2-type disease with allergies and asthma and increased biomarker levels, including serum IgE, thymic stromal lymphopoietin, and cutaneous

T cell-attracting chemokines, were also more likely to have severe skin disease complicated by eczema herpeticum (EH), *Staphylococcus aureus*, or molluscum infections.²⁵ In addition, patients with *FLG* mutations have been found to have an increased risk for EH, a serious complication of AD.²⁶ It is worth noting that the epidermal differentiation complex, a candidate gene region for AD localized on chromosome 1q21, includes a number of other genes encoding structural proteins of epidermal cornification, including S100A proteins, small proline-rich region proteins, and late envelope proteins.²⁷ Using a proteomics approach, Howell et al²⁸ identified S100/A11 as a target in T_H2 cytokine-mediated inhibition of filaggrin and the antimicrobial peptide human b-defensin (HBD) 3 expression in AD skin, pointing to immune dysregulation affecting both epidermal barrier integrity and innate immune response. Still, the relationship of the skin barrier and immune abnormalities to the increased susceptibility to microbial colonization and infections remains to be fully elucidated.²⁹ Of interest, emerging observations that topical calcineurin inhibitors can in part correct the barrier defect in patients with AD and that gentamicin can restore the production of functional filaggrin chains provides further evidence of the complex relationship of the epidermal barrier and the immune system.³⁰ Although future studies might shed further light on unique AD phenotypes and a more individualized approach to care, at present, a comprehensive, multipronged treatment approach addressing both the epidermal barrier and immune dysregulation is most likely to result in disease control for our patients.³¹

AD: IS PREVENTION POSSIBLE?

A recent review addressed the subject of therapeutic attempts to shift the presumed T_H2 response early in life to a T_H1 response through the administration of probiotics to pregnant women and subsequently to at-risk newborns either to prevent AD or even to treat established AD.³⁰ Although 1 meta-analysis suggested a modest role for probiotics in children with moderately severe disease in reducing the Scoring of Atopic Dermatitis Severity Index score,³² another found that current evidence is more convincing for the efficacy of probiotics in the prevention rather than treatment of pediatric AD.³³ In contrast, a study designed to replicate an earlier one that showed beneficial effects of probiotics in patients with AD found that supplementation with *Lactobacillus GG* during pregnancy and early infancy neither reduced the incidence of AD nor altered the severity of AD in affected children but was associated with an increased rate of recurrent episodes of wheezing bronchitis.³⁴ Furthermore, a recent Cochrane review concluded that probiotics are not an effective treatment for eczema in children and that probiotic treatment carries a small risk of adverse events.³⁵ Salfeld and Kopp³⁶ recently reviewed this subject, pointing to flaws in the methodology of some of the analyses and the heterogeneity of treatment protocols. They concluded that selection of the most beneficial probiotic strain or strains, use of probiotics with or without prebiotics, and timing of supplementation, along with optimal dose and delivery, remain to be determined. Thus probiotics for the prevention of AD remain investigational and, at present, cannot be recommended for primary prevention.

AD: MOVING BEYOND THE T_H1/T_H2 PARADIGM

A role for new subsets of T cells in patients with AD is being increasingly appreciated. Naturally occurring CD4⁺CD25⁺

forkhead box protein 3 (FoxP3)-expressing regulatory T (Treg) cells with normal immunosuppressive activity appear to be expanded in the peripheral blood of patients with AD.³⁷ However, after stimulation by the superantigen (SAg) staphylococcal enterotoxin B (SEB), Treg cells lose their immunosuppressive activity, suggesting a novel mechanism by which SAGs could augment T-cell activation in patients with AD.³⁸ Hijen et al³⁹ recently confirmed increased numbers of Treg cells found in the peripheral blood of patients with AD and hypothesized that this was due to strong inflammatory signals, with Treg cell suppressive activity subverted by proinflammatory mediators. Verhagen et al⁴⁰ showed CD4⁺CD25⁺FoxP3⁺ Treg cells were not found in lesional AD skin or in atopy patch test sites of patients with AD. Thus a dysregulation of disease causing effector T cells is observed in AD lesions in association with an impaired CD4⁺CD25⁺FoxP3⁺ Treg cell infiltration.

In addition, IL-17-secreting T_H17 cells in patients with AD have been investigated in several studies. IL-17 was first shown to be preferentially increased in acute versus chronic AD lesions.⁴¹ In a murine epicutaneous antigen challenge model analogous to human AD, IL-17 expression was induced not only in the skin but also in the airways.⁴² Using a murine model of filaggrin deficiency to examine whether this abnormality predisposes to skin inflammation and epicutaneous sensitization with protein antigen, this group also showed that filaggrin-deficient mice exhibited T_H17-dominated skin inflammation and eczematous changes with increased expression of IL-17 in the epidermis and increased antigen-specific IgE levels in their serum.⁴³ In an atopy patch test model IL-17 secretion was shown to be enhanced by SEB.⁴⁴ Induced IL-17 upregulated the antimicrobial peptide HBD-2 in human keratinocytes *in vivo*, although coexpressed IL-4/IL-13 partially inhibited this effect. Thus although IL-17-secreting T cells appear to infiltrate acute AD lesions and IL-17 secretion can be triggered by SAGs, subsequent ineffective IL-17-dependent upregulation of HBD-2 in patients with AD might result from partial inhibition by the T_H2 cytokine milieu. A study in IL-4 and IL-13 knockout mice supports a role for IL-4 as a T_H2 cytokine that downregulates the IL-17 response in epicutaneously sensitized mice.⁴⁵ This in turn could be one reason why patients with AD remain colonized by *S aureus*. Other investigators have also found that compared with skin of patients with psoriasis, T_H17 cells appear to have a diminished role in AD skin and that the associated reduced expression of innate defense genes might contribute to the increased skin infections seen in patients with AD.⁴⁶

THE ITCH-SCRATCH CYCLE IN PATIENTS WITH AD

Pruritus is a major symptom of AD and affects the quality of life of patients in a significant manner. The clinical observation that pruritus in patients with AD is often not relieved by antihistamines suggests that mediators other than histamine, such as cytokines and neuropeptides, might be involved.⁴⁷ IL-31, a cytokine that is increased in AD skin lesions,⁴⁸ has been implicated in the development of chronic dermatitis in transgenic mice that overexpress IL-31 through induction of severe pruritus.⁴⁹ Proposed sources of IL-31 include skin-infiltrating CLA⁺ T cells and peripheral blood CD45RO CLA⁺ T cells.⁵⁰ Recent data provide evidence that, irrespective of the atopic phenotype, serum IL-31 levels correlate with disease activity in patients with AD.⁵¹ Importantly, staphylococcal SAGs have been shown to rapidly induce *IL31* mRNA expression in the skin of atopic subjects *in vivo* and in

PBMCs *in vitro*, suggesting that chronic colonization and superinfection by *S aureus* can contribute to pruritus and inflammatory changes in patients with AD.⁴⁸ Given that pruritus in patients with AD is often resistant to antihistamines, IL-31 represents a potential target for antipruritic and anti-inflammatory measures in the treatment of AD. Gutzmer et al⁵² recently reported that the H4 histamine receptor (H4R) is upregulated on T_H2-type cells, suggesting a role for the H4R in a T_H2 milieu. Of note, they showed that H4R stimulation led to upregulation of IL-31, and stimulation of PBMCs with H4R ligand plus SEB resulted in higher *IL31* mRNA levels. These observations suggest a link between histamine and induction of pruritus, especially in patients with AD, and that the H4R represents a potential therapeutic target.

Another mechanism for chronic inflammation in patients with AD driven by immune dysregulation is an autoimmune model. The itch-scratch cycle can lead to damage of the epidermal keratinocytes and release of intracellular antigens, which in a subset of patients with AD could lead to a chronic autoreactive form of AD even without exposure to allergens.⁵³ Altrichter et al⁵⁴ recently found that sera from 28% of patients with AD showed IgE autoreactivity directed against epidermal or epithelial cell line-derived proteins, including cytoplasmic and cell membrane-associated moieties. This autoreactivity in patients with AD was significantly correlated with the severity of the disease, as defined by total serum IgE levels and clinical scoring indexes.

AD AND MICROBES

Patients with AD have a unique propensity to be colonized or infected by a number of microbial organisms (Fig 1). Dysregulation of the adaptive immune response with increased total and specific IgE levels has been associated with disease severity and infectious complications.^{2,55,56} More recently, the contribution of innate immune system abnormalities, including reduction in antimicrobial peptide levels, diminished recruitment of cells (eg, neutrophils) to the skin, and Toll-like receptor defects⁵⁷ and epidermal barrier abnormalities¹² in microbial colonization or infection in patients with AD, were the subjects of comprehensive reviews. As one example of the relationship between innate and adaptive immune responses and infectious complications of AD, both mobilization of HBD-3 and killing of *S aureus* by keratinocytes from patients with AD were shown to be significantly inhibited by the T_H2 cytokines IL-4 and IL-13, whereas neutralization of these cytokines significantly improved these activities.⁵⁸ In another example, serum IgE levels in patients with AD with herpes simplex virus (HSV) infections were found to be inversely correlated with cathelicidin LL-37 expression.⁵⁹ How aberrations in adaptive and innate immune responses and barrier abnormalities all interact in patients with AD remains to be fully investigated. Further insights might come from studies of patients with immunodeficiency with an AD-type cutaneous phenotype. Of interest, a recent study looking at a group of patients with poorly characterized combined immunodeficiency whose clinical presentation included recurrent cutaneous infections with *S aureus* or HSV and who also had increased serum IgE levels and eczematous rash found homozygous or compound heterozygous deletions and point mutations in the gene encoding the dedicator of cytokinesis 8 protein, leading to absence of dedicator of cytokinesis 8 protein in lymphocytes.⁶⁰

S aureus can be cultured from 90% of skin lesions and importantly can colonize normal-appearing skin in patients with AD.⁶¹



FIG 1. A, Child with AD superinfected with toxin-secreting *Staphylococcus aureus*. B, Child with AD with course complicated by EH.

Patients with more severe disease have been shown to have higher levels of *S aureus* in their home environments.⁶² *S aureus* can exacerbate or contribute to persistent skin inflammation in patients with AD by secreting toxins with superantigenic properties,

resulting in marked activation of T cells and other immune cells. Application of SEB to the skin can induce eczematous changes accompanied by infiltration of T cells selectively expanded in response to the SAg.⁶³ In addition, patients with AD can make

specific IgE antibodies directed against the toxins found on their skin, with basophils from these patients releasing histamine on exposure to the relevant toxin.^{64,65} This suggests that SAGs can induce mast cell degranulation after penetrating the epidermal barrier and contribute to pruritus and acute inflammatory events along with participating in chronic skin inflammation. *S aureus* isolates from patients with steroid-resistant AD have been shown to produce increased numbers of SAGs compared with isolates from control subjects.⁶⁶ Thus SAGs might offer a selective advantage for colonization of patients.

Other products of *S aureus* likely contribute to disease in patients with AD. Recently, children with impetiginized AD were found to have increased levels of lipoteichoic acid (LTA) that correlated with lesional Eczema Area and Severity Index scores and *S aureus* colony-forming units.⁶⁷ The amounts of LTA in the skin lesions were sufficient to exert biologic effects on various cell types *in vitro*, as well as epidermal cytokine gene expression when skin was exposed to LTA *ex vivo*. This study provides a further mechanism by which *S aureus* can exacerbate AD.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as an important pathogen that has rapidly evolved from a cause of nosocomial to community-acquired infections (see the review by Schlievert et al⁶⁸ in this issue). MRSA invariably produces SAGs. Wang et al⁶⁹ identified a novel class of secreted *S aureus* peptides, phenol-soluble modulins, that contributes to the enhanced virulence of community-acquired (CA) MRSA. These peptides appear to target neutrophils, recruiting, activating, and then lysing these cells. They also showed that the phenol-soluble modulins are under the regulatory control of the accessory gene regulator (*agr*) quorum-sensing system, which controls the expression of a number of staphylococcal virulence factors. Patients with AD might be particularly susceptible to colonization and infection by MRSA, as well as to the acute and chronic consequences of the SAGs that these organisms produce, because they are frequently treated, often for extended courses, with anti-staphylococcal antibiotics.⁷⁰ However, the question of whether patients with AD serve as an important reservoir of MRSA in the community has not been thoroughly investigated.⁷¹ Understanding the underlying mechanisms for infection and colonization by *S aureus* of the skin of patients with AD, including differences between methicillin-sensitive *S aureus* versus MRSA, is critical for developing more effective treatment strategies for this serious public health problem.

The clinical course in patients with AD can also be complicated by both localized and disseminated cutaneous viral infections, most often caused by HSV, human papilloma virus, or molluscum virus.⁷² EH is a potentially life-threatening disseminated HSV-1 or less commonly HSV-2 infection that occurs in 10% to 20% of patients with AD.⁷³ Risk factors for EH include early onset of AD, severe and untreated AD, head and neck dermatitis, previous EH or HSV infections, and increased total serum IgE levels with higher levels of specific sensitizations, especially against *Malassezia sympodialis*.^{73,74} Recent studies from the National Institutes of Health/National Institute of Allergy and Infectious Diseases Atopic Dermatitis and Vaccinia Network (ADVN) showed that when compared with patients with AD without a history of EH, patients with AD and EH have a more severe T_H2-polarized disease with greater allergen sensitization, including to staphylococcal toxins, and are also more likely to experience cutaneous infections with *S aureus*.²⁵ In addition, patients with AD of both European and African ancestry with the R501X mutation in

FLG have been found to have an even greater risk for EH, suggesting that a defective skin barrier can also contribute to this serious complication.²⁶ Importantly, patients with AD are also at risk for potentially life-threatening complications from both smallpox infection and from vaccinia virus (VV; eczema vaccinatum) used to prevent smallpox.^{75,76} When skin biopsy specimens from patients with AD are inoculated with VV, there is increased viral replication compared with that seen in healthy control subjects.⁷⁷ In addition, levels of the antimicrobial cathelicidin LL-37 are low, whereas expression of IL-4 and IL-13 is increased in AD skin, and antibodies against these T_H2 cytokines inhibit vaccinia growth and enhance production of LL-37. Of clinical importance, such studies might provide insights into identifying subjects who are at greatest risk for complications from immunization with VV.

BACTERIAL COLONIZATION AND INFECTION IN AD: TO TREAT OR NOT TO TREAT (WITH ANTIBIOTICS)

It is important to recognize that *S aureus* is a common commensal organism in human subjects and can be cultured from nonlesional skin in a significant number of patients with AD (see the review by Schlievert et al⁶⁸ in this issue). Colonization by toxin-secreting *S aureus* can contribute to pruritus and persistent inflammation.⁶⁴ In addition, colonization is a risk factor for infection.⁷⁸ Nevertheless, a number of factors contribute to difficulties in implementing successful strategies to clear colonization. *S aureus* can be found in the house dust of most patients with AD, and patients with more severe disease have higher levels of *S aureus* in their home environment.⁶² Patients treated with antibiotics quickly become recolonized, often with the same toxin-secreting organisms.⁷⁰ Family members often serve as the source of rapid recolonization.⁷⁹ Of note, in the recent study by Huang et al,⁸⁰ even after 3 months of twice-weekly dilute bleach bath therapy and monthly 5-day courses of nasal mupirocin, patients were still colonized by *S aureus*. Furthermore, the authors of a Cochrane Database systematic review did not find clear evidence of benefit for antimicrobial interventions in patients with AD. However, they point out that the studies were small and poorly reported and might not have shown the anticipated benefit.⁸¹

Given the complex pathophysiology of AD, a multipronged approach directed at healing or protecting the skin barrier and addressing the immune dysregulation will improve the likelihood of successful outcomes. This includes proper skin hydration and identification and elimination of flare factors, such as irritants, allergens, infectious agents, and emotional stressors, addressing the itch-scratch cycle, as well as pharmacologic therapy (reviewed in depth by Boguniewicz et al³¹). In theory, use of topical inhibitors of proteases should be an effective treatment strategy in patients with AD. To date, however, several trials with these agents have yielded disappointing results.³¹ An important concept with therapeutic implications is the recognition that normal-appearing skin in patients with AD is not immunologically normal.⁸² Furthermore, increased binding of *S aureus* to AD skin is related to underlying skin inflammation,⁶¹ and anti-inflammatory treatment with topical steroids and calcineurin inhibitors reduces *S aureus* colonization.⁸³ One approach to patients whose eczema tends to relapse in the same location is that of proactive therapy. After a period of stabilization, topical steroids^{84,85} or calcineurin inhibitors⁸⁶⁻⁸⁸ are applied to areas of previously involved but normal-appearing skin rather than

waiting for eczema to flare. Importantly, proactive therapy is an attempt to control residual disease because even normal-appearing skin in patients with AD might be colonized by *S aureus* and is characterized by immunologic abnormalities and not the application of an active drug to nonaffected skin.⁸⁹ Other approaches include silver-impregnated clothing, which has been shown to reduce staphylococcal colonization, improve clinical parameters, and reduce topical steroid use in patients with AD.^{90,91} High-dose intravenous immunoglobulin (IVIG) could have immunomodulatory effects in patients with AD, and in addition, IVIG could interact directly with microbes or toxins involved in the pathogenesis of AD. IVIG has been shown to contain high concentrations of staphylococcal toxin-specific antibodies that inhibit the *in vitro* activation of T cells by staphylococcal toxins.⁹² Treatment of severe refractory AD with IVIG has yielded conflicting results. Studies have not been controlled and have involved small numbers of patients.⁹³ Children appear to have a better response than adults. However, controlled studies are needed to answer the question of efficacy in a more definitive manner. New strategies might evolve from an important ongoing project looking at skin microbial flora with molecular rather than traditional microbiologic tools.⁹⁴

Abscesses associated with MRSA generally respond to drainage, and most CA-MRSA isolates are susceptible to trimethoprim-sulfamethoxazole or tetracycline, although obtaining cultures and sensitivities is important. Rifampin has been used in combination with other antibiotics but should never be used alone to treat staphylococcal infection. Other options include vancomycin, fluoroquinolones, daptomycin, newer-generation carbapenems, and linezolid.⁹⁵ In a study of children with culture-proved CA-MRSA, treatment with incision and drainage without adjunctive antibiotic therapy was effective management of skin and soft tissue abscesses with a diameter of less than 5 cm in immunocompetent children.⁹⁶ Extensive practical information on isolation of patients with MRSA and other practical issues can be found on the Center for Disease Control and Prevention's Web site (www.cdc.gov/ncidod/dhqp/ar_mrsa.html).

EFFECTS OF TOPICAL THERAPY ON SKIN BARRIER IN AD

A recent study looking at children with AD versus children with other atopic diseases and nonatopic control subjects confirmed that skin barrier function, as assessed by transepidermal water loss (TEWL), is intrinsically compromised in children with AD but not in children with other allergic conditions.⁹⁷ In addition, the authors showed that TEWL was higher in white children than in African American children with AD and that the magnitude of skin barrier dysfunction correlated with disease severity. Although TEWL might be a useful biomarker in patients with AD, racial and pigmentation differences will need to be considered. More recently, Jensen et al⁹⁸ looked at TEWL, as well as several other parameters of the epidermal barrier, including stratum corneum hydration and dye penetration, and showed improvement in all parameters when patients with AD were treated with both a topical steroid (betamethasone valerate 0.1% cream) and a topical calcineurin inhibitor (pimecrolimus 1% cream) applied to paired lesions of the upper extremities. Electron microscopic evaluation of barrier structure showed prevalently ordered stratum corneum lipid layers and regular lamellar body extrusion in the calcineurin inhibitor-treated skin but inconsistent

extracellular lipid bilayers and only partially filled lamellar bodies in the steroid treated skin. Both treatments normalized epidermal differentiation and reduced epidermal hyperproliferation. Betamethasone valerate was superior in reducing clinical symptoms and epidermal proliferation, but twice-daily use over the 3-week period of the study led to epidermal thinning. The authors concluded that because pimecrolimus improved the epidermal barrier and did not cause atrophy, it might be more suitable for long-term treatment of AD. However, the fact that the topical steroid was more effective in reducing clinical symptoms and inflammation supports the use of topical steroids for acute intervention of AD flares.⁹⁹

DEALING WITH VIRAL AND FUNGAL COMPLICATIONS

It is important for clinicians to be aware of the possibility of HSV complicating AD, especially EH. Vesicular lesions are umbilicated, tend to occur in crops, and often become hemorrhagic and crusted. Lesions can coalesce into large denuded areas. HSV might be misdiagnosed as impetigo, although herpetic lesions can become superinfected.¹⁰⁰ The presence of punched-out erosions, vesicles, and/or infected skin lesions that do not respond to oral antibiotics should prompt a search for HSV by using PCR, viral culture, or Giemsa-stained Tzanck smear of cells scraped from the base of a freshly unroofed vesicle. Treatment might be with oral acyclovir or other antiviral agents, such as valacyclovir for less severe infections or intravenous acyclovir for widely disseminated disease or toxic-appearing patients.⁷² Ophthalmologic consultation should be obtained for patients with periocular or suspected eye involvement. Lumbar puncture should be considered if meningitis is suspected, but the presence of infected lesions over the lumbar areas precludes this procedure. Antiviral prophylaxis might be necessary for patients with recurrent herpetic outbreaks.

Fungi can also play a role in the chronic inflammation seen in patients with AD. IgE antibodies against *M sympodialis* are found in patients with AD, most frequently in patients with a head and neck distribution of dermatitis.² However, even patients with IgE antibodies to *M sympodialis* often respond better to topical steroids than to topical antifungal therapy, and systemic antifungal therapy might benefit patients with AD through anti-inflammatory properties.

NOVEL DIRECTIONS IN THERAPY

Vitamin D deficiency is being increasingly recognized in the US population and might play a role in allergic illnesses.¹⁰¹ Importantly, vitamin D might play an important role in the regulation of antimicrobial peptides in keratinocytes.¹⁰² A trial with oral vitamin D in patients with AD supports this hypothesis.¹⁰³ In addition, in one small pediatric study children with AD treated with oral vitamin D in a randomized controlled trial showed improvement in the Investigator Global Assessment score in 4 of 5 subjects treated with vitamin D versus 1 of 6 subjects receiving placebo.¹⁰⁴ Similar changes favoring vitamin D therapy were also seen in the Eczema Area and Severity Index score. Larger ADVN-sponsored trials with oral vitamin D are currently in progress.

The emergence of CA-MRSA has created an urgency to develop novel strategies to combat this microbial organism. The best studied and probably most important virulence regulator in

staphylococci is the accessory gene regulator *agr*.¹⁰⁵ Of note, strong expression of *agr* appears to be an important characteristic of CA-MRSA strains.¹⁰⁶ *Agr* signals through an exported autoinducing peptide (AIP), and administration of an inhibiting AIP together with an infectious strain leads to a significant reduction in *S aureus* infectivity in a murine subcutaneous infection model.¹⁰⁷ In a novel approach Park et al¹⁰⁸ reported on the use of anti-AIP antibodies to inhibit *agr* function, demonstrating that antibodies designed against the AIP of one *S aureus agr* subgroup specifically prevent *agr* expression and *S aureus* disease in an animal model of abscess formation. These antibodies also provided protection when used for passive immunization (ie, when administered before infection). Although these findings provide cautious optimism in describing a successful strategy versus this key staphylococcal virulence regulator, it is worth noting that inhibition of the *agr* regulator in staphylococcal organisms results in upregulation of other virulence factors that are under opposite regulation by *agr*.¹⁰⁹ An important consideration in devising new therapeutic strategies against *S aureus* is recognizing that protective immunity to staphylococcal infections does not appear to exist to any significant degree, partly because of the fact that our immune system is in constant contact with staphylococcal antigens and because many strains are commensal organisms. In addition, *S aureus* produces protein A to help it evade acquired host defense. Although several attempts to develop protective vaccines have met with failure in clinical trials (eg, StaphVax), promising results based on using a combination of systematically selected antigens have been reported.¹⁰⁵ These combinatory vaccines target microbial surface components recognizing adhesive matrix molecules, a family of bacterial proteins that bind to human extracellular matrix components. Stranger-Jones et al¹¹⁰ developed a vaccine based on a combination of antigens that provided complete protection from lethal doses of *S aureus* in a murine challenge model. Importantly, microbial surface components recognizing adhesive matrix molecule vaccines have been shown to prevent colonization.¹¹¹ Whether this will result in decreased infection rates remains to be determined. Another potential antigenic target for vaccine development against *S aureus* is teichoic acid, which has been implicated in nasal colonization and biofilm formation.¹¹² Of note, a recent study in children with impetiginized AD found significant levels of LTA in infected lesions that were able to induce epidermal cytokine gene expression *ex vivo*.⁶⁷ A new conjugated vaccine (PentaStaph; Nabi Biopharmaceuticals, Rockville, Md) that includes both a-toxin and Pantone-Valentine leukocidin is currently in clinical trials.

A novel approach in dealing with staphylococcal toxins involves engineering binding affinity agents capable of neutralizing these SAGs. Soluble forms of the engineered Vb proteins produced in *Escherichia coli* were shown to be effective inhibitors of SEB-mediated T-cell activation and completely neutralized the lethal activity of SEB in animal models.¹¹³ More recently, the same group was able to express Vb domains in tandem as a single-chain protein and neutralized the clinically important SAGs SEB and toxic shock syndrome toxin-1 with a single agent, demonstrating the feasibility of engineering a broader spectrum antagonist capable of neutralizing multiple toxins.¹¹⁴

NEW ANTIVIRAL STRATEGIES

Given the post-9/11 concerns about use of smallpox and other agents as weapons of bioterrorism and the unique susceptibility of

patients with AD to serious adverse effects from vaccination with VV, novel approaches in protecting or treating a vulnerable population are urgently needed.^{75,76} With this goal, the National Institutes of Health established the ADVN. The increased propensity of patients with AD toward eczema vaccinatum might be related to a deficiency of antimicrobial peptides.^{77,115} Although cathelicidins and HBD-3 exhibit potent antiviral activity against VV,¹¹⁶ their use as anti-VV agents is limited due to rapid degradation by endogenous tissue proteases. Ceragenins are synthetic antimicrobial compounds designed to mimic the structure and function of endogenous antimicrobial peptides.¹¹⁷ They have been shown to disrupt bacterial membranes without damaging mammalian cell membranes.¹¹⁸ Of note, because of their synthetic nature, ceragenins are not subject to human protease degradation and therefore have a longer tissue half-life. Recently, investigators at National Jewish Health and Brigham Young University showed that one candidate compound (CSA-13) exhibits potent antiviral activity against VV through direct antiviral effects and through stimulation of the expression of endogenous antimicrobial peptides with known antiviral activity.¹¹⁹ They also demonstrated that topical application of CSA-13 was able to reduce satellite lesion formation, suggesting that treatment with CSA-13 might be an intervention for patients with disseminated VV skin infection.

KEY TAKE-HOME MESSAGES FOR CLINICIANS

Clinicians caring for patients with AD need to understand the important relationship between skin barrier abnormalities and immune dysregulation in this common but complex disease. They need to appreciate the strong association between *FLG* mutations and early-onset, persistent severe AD and the association with allergic sensitization and asthma. Furthermore, it is important to recognize the unique propensity for patients with AD to be colonized or infected by microbes, especially toxin-secreting *S aureus*, including MRSA, as well as HSV. Management needs to be directed at basic skin care, including repair and protection of the skin barrier with proper hydration and topical therapy, which includes both moisturizers and anti-inflammatory medications. Of note, these measures reduce microbial colonization and decrease the need for specific antimicrobial therapy, even in patients colonized by MRSA. In patients suspected of having an infectious complication of AD, obtaining culture and sensitivities from patients with difficult-to-treat AD can help identify resistant organisms and direct antimicrobial therapy, if needed. In addition, culture or PCR can identify HSV, which is often missed, especially if superinfected by *S aureus*. Identification and avoidance of irritants and proved allergens can further decrease skin inflammation and lessen the need for medications. Breaking the itch-scratch cycle and addressing sleep disturbance together with education are critical components of successful management of AD. Proactive treatment with topical steroids or calcineurin inhibitors in patients with recurrent AD involves application of medication 2 to 3 times weekly to previously involved but normal-appearing skin, recognizing that normal-appearing skin in patients with AD is not immunologically normal and is often colonized by *S aureus*. Although this approach has been shown to decrease flares over extended periods of time, it would currently be considered off-label therapy. EH is potentially a medical emergency, and patients might require intravenous antiviral therapy, as well as assessment for ocular involvement. With the

reintroduction of smallpox vaccination, clinicians should also be vigilant of the possibility of eczema vaccinatum in any patient with AD who has had recent close contact with another subject who has been immunized with this live viral vaccine.

What do we know?

- AD is a global health problem strongly associated with asthma and allergic sensitization.
- Compared with patients with AD without *FLG* mutations, those patients with AD who have mutations in *FLG* have disease that is earlier in onset, more severe, and more persistent and more likely to be associated with asthma and allergic sensitization.
- Most patients with AD are colonized by toxin-secreting *S aureus*, even on normal-appearing skin.
- Patients with AD with *FLG* mutations have been found to have an increased risk for eczema herpeticum.
- Topical anti-inflammatory measures can reduce *S aureus* colonization.

What is still unknown?

- The exact relationship between barrier dysfunction and immune dysregulation in patients with AD.
- What other skin barrier proteins besides filaggrin are essential for normal barrier function?
- A full understanding of why patients with AD compared with other inflammatory dermatoses have more problems with microbial colonization and infection.
- Specific biomarkers for AD and unique phenotypes.
- Optimal individualized therapy.

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