

MOC-CME Review

Clinical approach to the patient with refractory atopic dermatitis



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Key Messages

The approach to refractory atopic dermatitis should include a step-wise approach to rule out other diagnoses, confirm adequate first-line therapy, and rule out exacerbating factors prior to implementing second-line therapies.

- Immunodeficiencies and skin disorders can mimic atopic dermatitis
- Topical skin care technique is paramount to prevent continual flares
- It is difficult to identify triggers unless the patient is cleared first
- Consider infection and allergens, but do not overlook scratching
- Consider addressing behavioral factors using a multidisciplinary approach

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Discuss diagnostic considerations in refractory atopic dermatitis
- Describe an approach to the management of refractory atopic dermatitis

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that affects 20% to 30% of children and 7% to 10% of adults.^{1,2} Most patients have atopic comorbidities, including food allergy, asthma, and allergic rhinitis. Nearly 50% of children with AD continue to have symptoms into adulthood.¹ Adult-onset AD is also increasingly being identified as a distinct subset of AD, and these patients are at risk for systemic complications, including rheumatoid arthritis and inflammatory bowel disease.³ AD has a considerable negative effect on quality of life and sleep because of intense pruritus.⁴ These patients are at risk for mental health disorders and psychological stress. The current review examines a systematic approach for management of patients who present with refractory AD.

Clinical Vignette

A 9-month-old boy presented to National Jewish Health with a history of severe refractory AD and recurrent skin infections. His

itchy, eczematoid rash began on his chest at 2 months of age and then spread to his entire body, most notably his face, by 4 months of age. The itching required him to be continuously restrained, causing delays in motor development. His previous treatments included several moisturizers, topical corticosteroids (TCSs), and 2 courses of oral corticosteroids. Oral antibiotics were given on several occasions for methicillin-sensitive *Staphylococcus aureus* (MSSA) skin infections. Before his evaluation at National Jewish Health, the patient was hospitalized for MSSA facial cellulitis, requiring intravenous clindamycin and methylprednisone. Previous specific IgE testing revealed sensitization to egg, milk, peanuts, soy, and tree nuts. Elimination of all these foods from his mother's diet while breastfeeding did not improve his AD.

On physical examination, the patient presented with excoriated, eczematous lesions that involved his face, chest, back, arms, and legs (SCORAD [Scoring Atopic Dermatitis], 57). The patient was very uncomfortable, with continuous serpentine motions to scratch his back, and scratched his face uncontrollably. The remainder of his examination findings were unremarkable.



Figure 1. Case with difficult to treat atopic dermatitis. Initial photograph on admission (A) and improvement on the body only after use of wet wraps (B). Difficult to treat eczematous lesion on the left arm. Initial photograph on admission (C) and improvement only after starting treatment with topical tacrolimus (D).

Swabs of eczematous lesions were sent for bacterial, fungal, and herpes simplex virus culture. The patient began a nurse-supervised skin care regimen with soaking baths for 10 minutes twice daily followed by a midpotency TCS ointment to eczematous lesions on the trunk and extremities twice daily, a low-potency TCS to his facial eczema, and moisturizing cream to all unaffected areas. Full body wet wraps were applied for the first 3 days, with wet wraps of the face continuing through day 5 of hospitalization. Cultures were positive for MSSA on the skin, and the patient completed a 10-day course of oral cephalexin.

Although his chest cleared rapidly during the first week (Fig 1A and B), a few patches on his arms (Fig 1C and D) and most of his face remained recalcitrant to corticosteroid treatment. Tacrolimus ointment, 0.03%, was started twice daily to corticosteroid-resistant areas. Given his history of skin infections, immunoglobulins were measured, and he was found to have undetectable IgG, which was confirmed on additional testing. The remainder of his workup findings other than an elevated IgE level were normal (eTable 1). Although the patient improved after starting tacrolimus therapy, his AD was persistent, so intravenous immunoglobulin (IVIG) at 600 mg/kg was trialed in the setting of absent IgG likely attributable to transient hypogammaglobulinemia of infancy (THI). The use of IVIG in AD and THI is controversial, but it did demonstrate some benefit for our patient. Behavioral methods to help control itch while weaning off restraints were instituted by a pediatric psychologist, and parents received hands-on education from nursing staff daily before discharge. After discharge, IVIG was given for only one additional 600-mg/kg dose. A follow-up IgG level after 6 months of not taking IVIG was 287 mg/dL, and the patient was doing well on intermittent medium-strength TCSs for acute flares that involved

his trunk and extremities. Topical calcineurin inhibitors (TCIs) were used for his face. He had reduced AD and scratching.

Differential Diagnosis of AD

Immunodeficiency as a Masquerader of AD

There are several points to consider in a patient refractory to AD therapy. Many different rashes can look like AD and do not respond to AD therapies. Therefore, it is imperative to assess the differential diagnosis (Table 1) before introduction of increasingly potent anti-inflammatory therapy to the management of AD.

Primary immunodeficiencies can masquerade as refractory AD (Table 1). The child in our vignette had a diagnosis of THI, which has been associated with severe AD.⁵ THI is characterized by IgG levels less than 2 SDs below the mean for age and normal B cells. Previous reports have stated that children with THI and severe AD respond to treatment with IVIG. A study of 13 children with THI and severe AD used IVIG, 600 mg/kg per month, and found a clear benefit; however, there was no control group.⁶ A separate case series of 6 patients with severe AD and THI also found significant benefit with IVIG at 400 mg/kg per month, but again with no control group for comparison and the duration of IVIG varied.⁵ Given the lack of well-controlled studies of IVIG treatment in AD, the risk-benefit of each case needs to be weighed individually.

Because of their association with high serum IgE levels and eosinophilia, the different forms of hyper-IgE syndrome (HIES) should be considered. Patients with severe AD, recurrent sinopulmonary infections, and abscesses may have autosomal-dominant HIES (also referred to as Job syndrome), autosomal-recessive HIES, or, more rarely, phosphoglucomutase 3 mutations. Unique features of Job syndrome include retained primary teeth, fractures in the absence of trauma, coarse facial features, and scoliosis. Job syndrome also presents with recurrent cold abscesses, skeletal abnormalities, chronic mucocutaneous candidiasis, and deep-seated *Staphylococcus aureus* infections and pulmonary pneumatoceles. Patients with the *DOCK8* gene often present with exaggerated AD and recurrent cutaneous viral infections.⁷ Autosomal-dominant HIES is the result of *STAT3* dominant-negative mutations.

The 2 most common forms of autosomal-recessive HIES are patients with mutations in *DOCK8* and defects in signaling protein tyrosine kinase 2. Like autosomal-dominant HIES, autosomal-recessive HIES can present with staphylococcal and fungal infections, high serum IgE levels, AD, and eosinophilia. However, autosomal-dominant HIES often do not have allergic symptoms, although their serum IgE is elevated, whereas autosomal-recessive HIES can present with severe allergies, including food-induced anaphylaxis and environmental allergies. Patients with autosomal-recessive HIES are also prone to severe cutaneous viral infections, including eczema herpeticum (EH), recalcitrant molluscum contagiosum, and warts. Phosphoglucomutase 3 mutations patients have less eosinophilia compared with those with *DOCK8* and Job syndrome and may have cutaneous leukocytoclastic vasculitis, neurocognitive impairment, and myoclonus.

Omenn syndrome is a rare inflammatory variant of severe combined immunodeficiency disorder that presents with severe AD, erythroderma, desquamitous alopecia, severe diarrhea, failure to thrive, lymphedema, and hepatomegaly.⁸ Most patients with Omenn syndrome will be identified at birth with neonatal genetic screening. Infants with immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome have a *FOXP3* gene mutation that presents with severe AD, erythroderma, food allergy, and diarrhea. X-linked syndrome is predominantly associated with autoimmune manifestations, most commonly type 1 diabetes mellitus.⁸ Other disorders to consider include Wiskott-Aldrich syndrome, Netherton syndrome (NS), and acrodermatitis

Table 1
Differential for Refractory Atopic Dermatitis

Diagnostic considerations	Diagnostic assessment
Primary immunodeficiencies	
Transient hypogammaglobulinemia of infancy	Low serum IgG, normal vaccine responses
Autosomal dominant hyper IgE syndrome (AD-HIES)	<i>STAT3</i> mutation
Autosomal recessive HIES	<i>DOCK8</i> mutation, <i>TYK2</i> mutation
Wiskott-Aldrich syndrome	<i>WASp</i> gene mutation
IPEX syndrome	<i>FoxP3</i> gene mutation
Severe combined immunodeficiency	Low lymphocyte count, poor immune function, various gene mutations including <i>ADA</i> , common gamma chain, <i>PNP</i> , others
Skin infection	
Bacterial (eg, <i>S aureus</i>)	Skin culture
Viral (EV, EH, EC)	Viral PCR, culture
Fungal (<i>Malassezia</i> , <i>Candida</i>)	Fungal culture, skin scraping for fungal hyphae
Exposures	
Irritants (eg, scratching, fragrances, wool)	History, patch testing
Food allergies	History, PST, IgE to food
Environmental allergies	History, PST
Other conditions	
Netherton syndrome	Bamboo hair, <i>SPINK5</i> gene mutations
Acrodermatitis enteropathica	Plasma Zinc levels, <i>SLC39A4</i> gene mutations
Filaggrin mutation	<i>FLG</i> null mutations
Contact dermatitis	Patch testing, improvement after allergen removal
Scabies	Skin scraping
Psoriasis	Clinical diagnosis
Erythroderma of other causes, including oral steroid withdrawal	Clinical diagnosis
Malignancies (eg, cutaneous T cell lymphoma)	Skin biopsy

Abbreviations: AD-HIES, autosomal-dominant hyper-IgE syndrome; *DOCK8*, dedicator of cytokinesis 8; EC, eczema coxsacki; EH, eczema herpeticum; EV, eczema vaccinatum; HIES, hyper-IgE syndrome; Ig, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PCR, polymerase chain reaction; *PNP*, purine nucleoside phosphorylase deficiency; PST, prick skin test; *TYK2*, tyrosine kinase 2.

enterohepatica. The triad of Wiskott-Aldrich syndrome is diarrhea, thrombocytopenia, and severe AD-like rash. Wiskott-Aldrich syndrome is an X-linked disorder (mutation in the Wiskott-Aldrich syndrome gene [Xp11.4-p11.21]).⁸ The rash of Wiskott-Aldrich syndrome is indistinguishable from severe AD, but bleeding diathesis is a key distinguishing feature.

The triad of NS is atopic diathesis, hair shaft deformities, and ichthyosis.⁹ NS is associated with a mutation in the *SPINK5* gene, which encodes serine protease inhibitor Kazal-type 5, also known as lymphoepithelial Kazal-type-related inhibitor. In the epidermis, lymphoepithelial Kazal-type-related inhibitor is involved in the regulation of desquamation via its ability to selectively inhibit the serine protease inhibitors kallikreins 5, 7, and 14. Infants with NS develop generalized ichthyosiform erythroderma early in life, and the classic hair shaft abnormality of easily broken hairs, trichorrhexis invaginata, or bamboo hair is pathognomonic. Finally, acrodermatitis enteropathica, caused by zinc deficiency attributable to an intestinal zinc transport mutation, can also present with severe AD-like rash but without significant eosinophilia or atopy. The rash develops over anogenital and periorificial areas as well as the scalp, extensors, and digits. Although not considered a significant immunodeficiency, acrodermatitis enteropathica can often present with secondary skin infections of *Candida albicans*, most commonly on the face and digits.

Other Considerations in the Differential Diagnosis

Many other skin disorders can mimic the appearance of AD (Table 1).⁹ Contact dermatitis is characterized by well-demarcated erythematous plaques with overlying vesiculation and a history of preceding contact with an allergen. The inflammation can extend beyond the area of exposure, and a history of allergen contact will not always be provided.¹⁰ Both scabies and molluscum contagiosum (MC) should be considered in refractory AD given their potential to mimic AD. Scabies presents as erythematous excoriated papules, often on the palms, soles, and diaper area in children and on the wrist, interdigital spaces, axilla, and waist in adults. Definitive

diagnosis of scabies can be made by microscopic visualization of the burrows to find mites, eggs, or excrement (scybala), and treatment usually consists of topical permethrin. MC is easier to identify given the classic translucent flesh-colored papules with an umbilicated center. Patients with MC can present with pruritic eczematous eruptions around papules and self-inoculation attributable to scratching is possible. However, treatment of MC is not always recommended given its self-limited nature and caustic treatment modalities.

Patients with *FLG* mutations can also present with severe AD.^{2,11} *FLG* is primarily expressed by keratinocytes in the stratum granulosum and is involved in the organization of keratin filaments in the stratum corneum and maintenance of natural moisturizing factor and pH.¹¹ The consequences of *FLG* mutations is increased water loss, increased allergen penetration, and microbial dysbiosis.² Although most patients with severe AD do not have an *FLG* mutation, they often have filaggrin deficiency attributable to underlying skin inflammation. Studies have found that interleukin (IL) 4, IL-13, IL-22, IL-31, and IL-33 downregulate filaggrin expression. Indeed, studies have found that anti-inflammatory therapies increase filaggrin expression in AD.

Fundamentals of Skin Barrier Care and Repair

After the diagnosis of AD is confirmed, proper topical skin care should be instituted (Fig 2). Almost 20% of AD with a history of moderate-to-severe AD unresponsive to TCSs will respond to TCSs while the patient is under medical supervision, suggesting an adherence problem.¹² First-line management of AD includes emollients, baths, and TCSs. Furthermore, education is paramount because poor technique can lead to continual flares. Observing patient application of skin products is mandatory in the refractory patient because it can provide an explanation for failed therapy. Observation can rapidly identify the patient who is resistant to bathing or patients who do not understand the nuances of topical therapies. For example, some patients place moisturizers directly over topical anti-inflammatories, thinking that it will increase penetration of

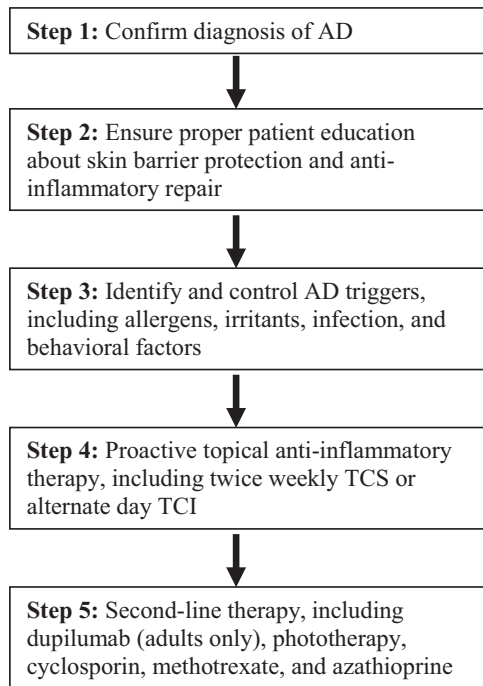


Figure 2. Approach to patient with atopic dermatitis (AD) who does not respond to routine skin care. TCI indicates topical calcineurin inhibitor; TCS, topical corticosteroid.

medications; however, so-called layering actually dilutes the potency of topical medications. Even with the correct diagnosis and adequate management, infection, exposures, scratching, and stress can cause continual flares.

Skin emollient therapy reduces the amount of TCSs needed to achieve control and has been shown to reduce pruritus.^{9,13,14} Randomized trials have demonstrated that emollients can preserve microflora diversity.¹⁵ Emollients also prevent AD in neonates.^{16,17} Even the emollient ingredient petrolatum alone has secondary anti-inflammatory and antimicrobial effects.¹⁸ Thus, adequate barrier therapy remains the cornerstone of AD treatment.^{13,19}

Although the type of moisturizer should be fragrance and preservative free and preferably an ointment to trap moisture, there is no clear evidence to support one brand over another.^{13,20} In severe AD, consider soaking the skin in warm water for at least 15 minutes and apply emollients immediately after a light pat dry to seal in moisture (ie, soak and seal).^{13,21} Bathing should be performed at least once daily, and the consensus is that more bathing is better when emollients are placed immediately afterward to prevent overdrying.²²

TCSs are highly efficacious for both acute flares and maintenance when used properly.^{13,19,20} TCSs have proven to be effective in the reduction of AD inflammation in more than 100 randomized clinical trials.^{13,20} Guidelines suggest twice-daily application with medium- to high-potency TCSs for several weeks for acute flares and tapering to twice weekly for proactive maintenance, particularly during seasons associated with frequent relapse, such as winter.^{13,20} High-potency TCSs should be avoided on sensitive areas, such as the face, neck, axilla, and groin, because of increased absorption at these sites. Steroid phobia is a common problem, and undertreatment can make even moderate AD look recalcitrant to therapy.

TCIs are a distinct class of steroid-sparing therapy for AD patients older than 2 years.¹³ TCIs offer the advantage of being safe on sensitive areas of the skin and are generally considered second-line topical anti-inflammatory therapy for AD.^{13,20} Application of the TCIs, both tacrolimus and pimecrolimus, are twice daily for acute

lesions with a taper to alternate days for proactive therapy. A key distinction from TCSs is that TCIs should not be used in conjunction with wet wrap therapy (WWT).^{13,20} Some cases of refractory AD may respond better to TCIs than TCSs as evidenced by a multicenter randomized clinical trial of steroid-resistant patients.²³ This is particularly true of facial or eyelid dermatitis where potency of TCSs are limited to low potency. Therefore, a brief trial of TCIs in the setting of poor response to TCSs may be warranted in refractory AD. Care should also be taken to describe the common localized site reactions, including burning, stinging, and pruritus, during the first few days of TCI therapy to prevent premature discontinuation.¹³ On the basis of a joint task force of the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology, current data do not support the use of a black box warning for TCSs, and off-label use in children younger than 2 years can be considered in refractory AD.²⁴

Crisaborole, recently US Food and Drug Administration (FDA) approved for use, is a topical phosphodiesterase (PDE) 4 inhibitor that has a favorable safety profile and overall efficacy in AD.^{25,26} Inhibiting PDE4 increases intracellular cyclic adenosine monophosphate, which reduces various inflammatory mediators, including tumor necrosis factor α , interferon (IFN) γ , IL-12, IL-17 and IL-23.²⁶ PDE4 inhibitors also limit pruritus, making them a therapeutic option for patients with mild to moderate AD who have secondary infections and sleep disturbance from chronic scratching.²⁷

The Multidisciplinary Approach to Management of Severe AD

When approaching a patient with refractory AD, it is important to ensure treatment failure is not attributable to behavioral factors, such as poor adherence, improper technique, sleep disturbance, depression, and other factors²⁸ (Table 2). Psychological stress can itself trigger itch, leading to a vicious cycle of AD flares. Sleep loss can negatively affect cognition, mood regulation, behavior, attention, and family dynamics.⁴ Therefore, behavioral interventions for stress, habitual scratching, and sleep disturbance can significantly improve quality of life and decrease reflares.⁴ Behavioral interventions that can considerably affect the itch-scratch cycle and the course of AD include habit reversal training; relaxation training, including biofeedback; and cognitive behavioral therapy, such as aversion techniques and operant conditioning.²⁸ Sleep hygiene

Table 2
Behavioral and Educational Reasons for Poor Responses

1. Confirm proper skin care
• Ensure proper technique with bathing, skin emollients, and TCS under supervision
• Consider TCIs or another anti-inflammatory nonsteroidal for steroid refractory AD
• Institute proactive TCS or TCI for chronic relapsing AD
• Inadequate quantity of applied topical medication
• Write clear therapy home management plan
2. Patient education on skin care
• Provide hands on education to show how much topical therapy to use and how exactly to apply
• Ensure proper placement of emollients on unaffected areas and TCS or TCIs on affected areas
• Do not mix or layer emollients and topical anti-inflammatory therapy
3. Patient education related to behavioral health
• Address psychosocial stressors that may affect habitual scratching, sleep, and adherence
• Educate on sleep hygiene and consider sedating antihistamines at night
• Provide methods to prevent habitual scratching such as habit reversal or relaxation techniques
• Provide clear school or day care guidelines to help facilitate treatment success away from home

Abbreviations: AD, atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

should be optimized as much as possible, which can be aided by the use of wet wraps or sedating antihistamines at night to prevent scratching.⁴

Many of these interventions are best served in a multidisciplinary setting to help control the different factors that trigger AD.²⁹ It is difficult to identify triggers, such as food allergy and stress, unless the patient is cleared and the trigger is reintroduced because it is difficult to interpret why a patient goes from bad to worse, whereas when a patient is cleared of skin disease, they are inherently free of other exacerbating factors, so the introduction of a culprit food or irritant is much easier to interpret in this controlled setting.

A multidisciplinary approach in a day hospital setting can provide comprehensive family education and unique services, such as behavioral health specialists, nutritionists, specialized nursing, dermatologists, and allergists. Given the time constraints of the modern allergy practice, nurse-led educational interventions, especially hands-on demonstrations for difficult treatments, such as wet wraps, can increase treatment adherence and success.^{21,29} Behavioral therapists, such as psychologists, can help families identify and break emotional triggers for the itch-scratch cycle, optimize sleep routines, and identify psychosocial barriers to therapy. A nutritionist can give dietary counseling to promote growth and to ensure adequate nutrition, which is especially important in patients with food allergies on elimination diets.

Exacerbating Factors

Irritants, allergens, and habitual scratching can continuously exacerbate AD therapy, preventing the success of otherwise suitable AD therapies. Although much of the focus of exacerbating factors is often placed on food and environmental allergens, irritants, such as heat, pollution, sweat, harsh fabrics (eg, wool and acrylic), or additives and fragrances in topical products, can play a role in refractory AD.²⁹ Often overlooked, scratching damages the epithelial barrier to increase inflammation and type 2 immune responses.

Food and environmental allergens may play a role in refractory AD, but caution should be exercised when interpreting allergy testing and recommending food avoidance.^{30–33} Patients with severe AD, particularly children, often have more food sensitization. However, food sensitization does not imply allergy without the correct clinical context. Although negative skin test results with proper controls have a high negative predictive value, positive blood testing results have a low specificity and low correlation with AD symptoms.^{20,21} Specific IgE blood testing to food allergens may be helpful to determine the probability of reaction for the major food allergens, but they do not determine the type or severity of the reaction. The 95% predictive decision point for passing an oral food challenge has only been well established for milk, egg, and peanut²¹; therefore, extensive food allergy panels are almost never warranted and often lead to unhealthy or even dangerous elimination diets. In a study of children with AD and food allergies, 89% passed oral food challenges to their positive food sensitizations.³⁴ Another double-blind study of placebo-controlled food challenges in children from 2001 to 2011 found that patients with AD are frequently asymptotically sensitized to foods.³² Clinical correlation with previous reactions and, more importantly, supervised oral food challenges are needed to confirm positive results because many food sensitizations are not clinically relevant.¹³

Aeroallergen sensitization is also more common in severe AD, but the association with clinical symptoms is not well established. Guidelines emphasize controlling for house dust mite and minimizing animal dander and pollen exposure when patients show positive sensitization.^{13,20} Allergen immunotherapy is generally not recommended for refractory AD based on available evidence,³⁵ with only moderate efficacy in randomized clinical trials mainly when used for house dust mite sensitization.³⁶

Management of Skin Infections

S aureus Infection and Colonization

Conventional therapies can fail in severe AD because of unmanaged infection or colonization with a variety of different organisms. Both lesional and nonlesional skin of patients with AD have higher *S aureus* levels compared with healthy controls, and this increased density is significantly associated with severe AD.³⁷ The type 2 mediated chronic inflammatory milieu, higher pH, suppression of antimicrobial peptides, and excessive expression of *S aureus* binding sites make patients with AD more prone to *S aureus* colonization and infection. IL-4 and IL-13 also increase keratinocyte susceptibility to the cytotoxic effects of α -toxin released by *S aureus* compared with IFN- γ and T_H1-mediated immune responses that confer protection.³⁸ *S aureus* release a number of other enterotoxins that can worsen AD, including staphylococcal enterotoxins A, B, C, and D and toxic shock syndrome toxin 1. Staphylococcal enterotoxin B increases IL-31, which induces pruritus. Taken together, the increased susceptibility to *S aureus* in patients with AD justifies a low threshold for obtaining cultures and antibiotic sensitivities in patients with severe refractory AD.

There are many important factors to consider in the role of *S aureus* in patients with severe AD.³⁹ *S aureus* colonization is observed in up to 90% of AD cases with active skin lesions and correlates with the level of AD treatment required. Type 2 immune response, including serum IgE levels and eosinophils, are also increased in patients with *S aureus* colonization.

S aureus decolonization is typically performed with bleach baths and/or topical mupirocin in the nares.^{13,40} Several clinical trials have demonstrated the efficacy of diluted bleach baths in AD given their ability to reduce *S aureus* colonization and anti-inflammatory effects.⁴¹ Therefore, in patients with methicillin-resistant *S aureus* (MRSA) or repeated MSSA infections, bleach baths should be considered with one-fourth to a half cup of household bleach per full tub of water, whereas topical mupirocin should be applied in the nares twice daily for 10 days, although studies have also cited 5 days as sufficient.²¹ Rinsing off after bleach baths can help prevent irritation, but overall they are well tolerated and do not lead to any ill effects on the skin barrier when used short term.⁴²

Systemic therapy, particularly when used empirically for bacterial colonization, is more controversial. The most recent systematic Cochrane review examined 26 trials, most of poor quality, and found mixed results, leading them to conclude that antibiotic treatment reduces *S aureus* load but may not improve outcomes.⁴³ Guidelines also suggest that systemic antibiotics are not recommended without evidence of bacterial infection.¹³ Repeated antibiotics increases the risk of MRSA. However, for patients with refractory AD without repeated antibiotics or MRSA infection, it may be pragmatic to treat while awaiting culture results simply based on their severity (Fig 3). Moderate-to-heavy growth of *S aureus* most closely associates with disease severity and correlates with affected lesion intensity and lichenification. In most cases, reduction of skin inflammation through the use of bathing, in combination with emollients and topical anti-inflammatory therapy, will significantly reduce *S aureus* colonization. In summary, the choice to initiate empiric antibiotic therapy should be based on clinical evidence of infection and positive culture results with antibiotic choice guided by local resistance patterns.

Viral Infections

Viral skin infections are less common than bacterial infections in patients with AD, but left untreated some viral infections can lead to systemic life-threatening illness. In patients with AD, antiviral plasmacytoid dendritic cell levels are decreased, and IL-4 and IL-13



Figure 3. Severe atopic dermatitis with methicillin-resistant *Staphylococcus aureus* (MRSA) skin infection. Initial photograph on admission (left) and after MRSA decolonization and supervised skin care in a multidisciplinary day program (right).

suppress antimicrobial peptides, which have potent antiviral activity.⁴³ Patients with AD and EH also have reduced expression of IFN- α , IFN- β , and IFN- γ and their receptors. *S aureus* superinfected viral lesions are common and require high suspicion in patients not responding to antibiotics. Unlike EH, eczema coxsackium (EC)⁴⁴ has been less studied and is not life-threatening; however, prompt confirmation of EC with lesional polymerase chain reaction for enterovirus is imperative because it can be mistaken for EH. EH can lead to several serious complications, including keratoconjunctivitis and meningitis, so empiric treatment while awaiting culture results or polymerase chain reaction may be warranted with clinical suspicion. Although oral acyclovir can be used in mild EH cases, there should be a low threshold for hospitalization and intravenous acyclovir in moderate-to-severe EH.

Eczema vaccinatum (EV) has historically followed smallpox vaccination in susceptible patients with AD or close contacts with someone who was recently vaccinated with the smallpox vaccine.⁴⁵ However, in areas where this vaccine is still given, it should be contraindicated in patients with AD unless they have exposure to smallpox whereby the benefits of the vaccine outweigh the risks of EV. For treatment of EV, recently documented cases have effectively applied a combination of vaccinia immunoglobulin with cidofovir and investigational drugs ST-246 and CMX001.⁴⁶

Fungal infections with *Malassezia* species and *Candida* species should also be considered in some refractory cases. Although the direct link between the commensal lipophilic yeast *malassezia* and increased inflammation is unclear, increased IgE sensitization may be a key factor.⁴⁷ A potassium hydroxide preparation for yeast, skin culture for fungi, and IgE to *Malassezia* testing should be considered in refractory AD cases.¹³ For the most part, *Malassezia* species are susceptible to azole antifungals, such as ketoconazole, in both the topical and systemic form, although there is more evidence for efficacy in the latter.⁴⁷ *Candida* species have also been implicated in patients with AD. Most studies of *Candida* in patients with AD have not seen an appreciable difference in colonization compared with healthy controls. Still, it has been postulated that the impaired immune response in AD may lead to inflammation from even normal levels of *Candida* species.⁴⁸

Alternative Approaches

Wet Wrap Therapy

When severe AD cannot be adequately controlled with topical therapies and avoidance of trigger factors, the use of WWT should be highly considered before systemic therapies.⁴⁹ WWT can also provide a physical barrier to scratching, which is particularly helpful in children to stop the itch-scratch cycle at night (Fig 4). WWT is best performed by covering a layer of TCS with a first layer of wetted clothing or bandages followed by a second dry layer (Fig 5). Caution should be taken not to perform WWT too often because patients can develop localized adverse effects, such as folliculitis and skin maceration.²⁰ The main barriers to WWT are the time it takes to properly teach the family and poor adherence because of application time and initial discomfort.⁴⁹

Role of Special Clothing

Although WWT can be highly effective in patients with severe AD because of increased absorption of moisturizers and topical corticosteroids, they also function as an effective barrier to irritants and scratching, especially overnight. However, the application of wet layers of clothing and the time commitment to apply WWT can be offputting to some patients. Development of special clothing with beneficial effects to the skin barrier are an active area of investigation. Such clothing includes fabrics made from silk (DermaSilk, Silk Skinnies), which can serve as an effective barrier to irritants and has additional benefits: breathability, a smooth nonirritating nature, and the capacity to be treated with various antimicrobial and water-resistant compounds.⁵⁰ Furthermore, studies have established the efficacy of silk clothing^{51,52} in AD, making it a potential consideration as alternative or adjunct therapy.

Systemic AD Therapies

Systemic therapies should only be considered after addressing the differential diagnosis, adherence to proactive topical anti-inflammatory care, infection, and other exacerbating factors.^{9,13}



Figure 4. Severe atopic dermatitis with significant signs of excoriation. Initial photograph on admission (left) and after wet wrap therapy (right).

Phototherapy should be considered when feasible before the initiation of treatment with systemic drugs, although this recommendation may change with the recent FDA approval of dupilumab for moderate to severe AD.⁵³ Numerous studies have established the efficacy of phototherapy with narrow band UV-B for chronic AD, UV-A for acute flares, and psoralen plus UV-A in widespread disease.^{13,54} The light modality chosen should be guided by cost, availability, skin type, and cancer history, with ongoing physician supervision required in all cases. Care should be taken to adjust dosing according to the minimal erythema dose and/or Fitzpatrick skin type. Common adverse effects include actinic damage, burning, and stinging. Although rare, nonmelanoma skin cancer and melanoma, particularly with the use of PUVA, have been reported.⁵⁴ Although useful in many cases, the availability and cost of phototherapy often make it unfeasible, leading physicians to consider more readily available systemic drugs. Unfortunately, systemic corticosteroids are often prescribed because they rapidly improve clinical symptoms and are easily attainable. Consensus guidelines and efficacy studies emphasize systemic corticosteroid use only in the context of bridging to another steroid-sparing treatment because of severe rebound flares after use.⁵⁴

A multicenter, double-blind, randomized trial in adults comparing oral cyclosporine, prednisone, and placebo was prematurely terminated because of rebound flare in the prednisone arm, and only 1 of 27 patients taking prednisone had durable remission.⁵⁵ On the other hand, oral cyclosporine revealed durable remission and was significantly more efficacious than prednisone and placebo, making it a better candidate as second-line systemic therapy.⁵⁵

Although efficacy has been shown in many adult trials, the dosage and duration of therapy vary widely. Some guidelines suggest a short course of approximately 6 months with 5 mg/kg daily for severe refractory AD.⁵⁴ A recent meta-analysis comparing 34 randomized clinical trials of 12 different systemic treatments concluded that only short-term cyclosporine could be highly recommended.⁵⁶ Small cohort data also suggest that long-term cyclosporine may lead to more relapse, but more studies are needed to substantiate these findings. Evidence in pediatrics has been less robust, with only small retrospective cohorts suggesting cyclosporine efficacy⁵⁷ and a suggestion that using a longer duration of lower dosages may

decrease relapse and adverse events in children. A recent randomized trial of young adults also found that concomitant topical therapy increased treatment success, emphasizing the importance of continuing first-line topical therapy even in the setting of systemic drugs.⁵⁸

Methotrexate, azathioprine, and mycophenolate mofetil have also been used as second- or third-line therapy in refractory AD but are not as well characterized as cyclosporine. The general mechanism of these drugs is to inhibit DNA synthesis of rapidly dividing cells by various actions: methotrexate blocks dihydrofolate reductase, azathioprine blocks purine synthesis, and mycophenolate mofetil inhibits inosine monophosphate dehydrogenase. Although one particular randomized trial found similar benefits between cyclosporine and methotrexate, the small sample size and lower than commonly used dosage for methotrexate make this trial less convincing. Furthermore, a meta-analysis comparing 34 randomized clinical trials found methotrexate and azathioprine a distant second and third choice, respectively, to cyclosporine.⁵⁶ Small retrospective trials for methotrexate have seen modest benefit in adults, with effective doses ranging from 7.5 to 25 mg but with varying routes, duration, and occasional dropouts attributable to gastrointestinal symptoms or transaminitis.⁵⁹ Evidence in children is even more limited, with only case reports showing methotrexate success in severe refractory AD. Azathioprine also has modest benefit in severe AD when compared with methotrexate. Before starting azathioprine treatment, thiopurine methyltransferase enzyme activity should be determined to identify slow metabolizers to adjust dosing to prevent toxicity while maintaining efficacy.⁶⁰ Despite adjustment based on thiopurine methyltransferase activity, the dosing and duration used still vary widely with increased adverse effects compared with methotrexate, including gastrointestinal symptoms, elevated liver enzymes, leukopenia, and hypersensitivity reactions.⁶¹ Studies of mycophenolate mofetil in adults have been small and retrospective, and data in children are even more limited.⁶⁰ However, mycophenolate mofetil has fewer side effects than methotrexate and azathioprine. With only modest benefits in adults and even less effective results in children, methotrexate, azathioprine, and mycophenolate mofetil should be considered second- or third-line therapy in refractory AD.^{13,56}



Figure 5. Wet wrap therapy procedure for entire body (can be adapted for individual areas as needed). Soaking bath for 15 to 20 minutes (A), apply topical corticosteroids to affected areas and emollients to unaffected areas on the face and body (B), dress in wet socks to hands and feet (C), dress in wet pajamas (D), place a second layer of dry socks over hands and feet (E), place a second layer of dry pajamas (F), place a wet layer of gauze around the face followed by a dry layer (G), be sure to leave space for the eyes, nose, and mouth (H).

Use of Biologics in AD

Biologics show great promise in future treatment of moderate-to-severe AD. Their use in severe AD is more extensively discussed in the review by Brunner et al⁶² in the current issue of the *Annals*. Given their targeted effects, not all biologics will be equally effective in different subsets of AD. As an example, omalizumab is a monoclonal antibody that binds free and membrane bound IgE, which decreases activation of the FcεRI receptor. An extensive meta-analysis of available randomized clinical trials, comparative studies, and case series found no evidence of clear benefit for omalizumab use in severe AD.⁶³ Similarly, there have been mixed results found for ustekinumab,⁶⁴ a monoclonal antibody that blocks IL-12 and IL-23, and rituximab, a monoclonal antibody to CD20.⁶⁵

Dupilumab is a monoclonal antibody that blocks the α -subunit of IL-4 receptor α , thus effectively blocking the actions of IL-4 and IL-13, which are key cytokines involved in the development of AD. Dupilumab has shown efficacy and an excellent side effect profile in phase 2 and 3 clinical trials for severe adult AD^{66,67} and was recently FDA approved in the management of moderate to severe AD. Although dupilumab seems highly effective in T_H2 -mediated AD, our

understanding of moderate to severe AD has evolved from “one-size fits all” to include several separate phenotypes and endotypes, which may require different therapeutic targets.^{68,69} Additional molecules in the pruritus pathway, IL-31 and the T_H2 skewed response in AD lesional skin, thymic stromal lymphopoietin, OX40, and the prostaglandin DP_2 receptor, are currently in early phase clinical trials.⁶² Related therapies include Janus kinase 1 and Janus kinase 2 inhibitors currently in phase 2 trials. Many of these therapies show promise and may be incorporated into treatment protocols after further efficacy studies and a better understanding of AD phenotypes and endotypes.⁶⁸

Conclusion

The 9-month-old boy with THI and AD in our vignette illustrates many of the challenges commonly faced by practitioners dealing with severe refractory AD. Although his rash appearance and food allergies made the diagnosis of AD very likely, we considered other diagnoses given his poor response to therapy. The first additional intervention that our patient received after a less than expected response to supervised emollients, TCSs, and wet wraps,

was a switch to TCIs for possible corticosteroid-refractory AD. We observed initial benefit from this change but continued investigating for other possibilities by obtaining several skin cultures and treating for MSSA with oral cephalexin. His history of frequent skin infections raised concern for immunodeficiency, and subsequent workup demonstrated an undetectable IgG. Although evidence is sparse, there has been some benefit in patients with refractory AD and THI who are treated with IVIG, albeit with longer durations than the 2 monthly doses that our patient received. The combination of oral antibiotics and IVIG provided additional benefit to our patient. The patient also benefited from our multidisciplinary approach with nurse- and physician-supervised treatments and behavioral health interventions to improve scratching, sleep, and the overall mental well-being of the family. Over time, continued use of emollients, TCIs, and as needed wet wraps with TCSs enabled our patient to improve and remain generally clear and unrestrained. This case highlights the importance of a multidisciplinary approach and continued investigation into infection, topical corticosteroid resistance, and the differential of refractory AD, including immunodeficiency. Although dupilumab would be a consideration in such severe forms of AD, dupilumab has not yet been studied or approved for use in children.

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Supplementary Data

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Supplementary Data

eTable 1

Key Immunologic Studies in Our Case

Test	Value	Reference range
IgG, mg/dL	<75	286-1,680
IgM, mg/dL	24	21-192
IgA, mg/dL	12	10-129
IgE, mg/dL	593	0-10
Total white blood cells, / μ L	10,000	5,000-13,000
Total lymphocytes, / μ L (%)	5,510 (55.1)	1,300-8,800
Total CD3 lymphocytes, / μ L (%)	3,642 (66.1)	1,900-5,900
Total CD19 lymphocytes, / μ L (%)	1,063 (49.3)	610-2,600
Total CD4 lymphocytes, / μ L (%)	2,716 (13.1)	1,400-4,300
Total CD8 lymphocytes, / μ L (%)	722 (13.1)	500-1,700
CD4/CD8 ratio	3.76	1.2-6.2
IgD ⁺ CD27 ⁺ B cells, %	3.7	1.6-4.1
IgD ⁺ CD27 ⁺ B cells, %	0.8	0.1-1.9
IgD ⁺ CD27 ⁻ B cells, %	93.7	90.9-96.2
CD4/CD45 RA T cells, %	76.8	64-93
CD4/CD45 RO T cells, %	21.2	5-18