Welcome to our first issue of Dermatology Nurse Practice
This is the first in a series of print and online educational resources that is being developed by the Dermatology Nurses' Association thanks to unrestricted educational grants from Incyte and Pfizer. We hope that you find the information in this and subsequent publications of informational and educational value as you progress in your career as a dermatology nurse. If there are topics you’d like to learn about in the future or if you have any feedback on this education, please don’t hesitate to drop us a note at dna@dnanurse.org. We’d love to hear from you!

INSIDE THIS ISSUE:
What is driving the increased prevalence of atopic dermatitis (AD) both in the United States and around the globe?
What are the differences between the “inside-out” and “outside-in” theories that have been proposed to help explain why AD develops in some individuals but not others?
How common is the “atopic march” among infants who are diagnosed with AD?
What are some of the more common pathways targeted by therapies commonly used to treat AD?

The Pathophysiology of Atopic Dermatitis:
A Nursing Primer

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LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

• Discuss the genetic and environmental factors that help drive the development of atopic dermatitis (AD)
• Describe the mechanisms of action by which specific nonpharmacologic and pharmacologic agents used in the treatment of AD impact the progression of disease
• Explain the primary components of the “atopic march”
• Identify key issues involved in the management of AD at various stages of life

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INTRODUCTION

Atopic dermatitis (AD) is an inflammatory, relapsing skin disease that typically—but not always—starts in childhood and is characterized by intense itching.\(^1\) It is a multifactorial and complex condition involving genetic alterations, disruption of the skin barrier, immune dysregulation, microbial dysbiosis, and environmental triggers. Patients typically experience xerosis (dry skin) and diffuse, reddened, itchy papules and plaques, which then become chronic lesions characterized by lichenification (thick, leathery skin), dyspigmentation, and fibrotic nodules (Figure 1).\(^2,3\)

AD negatively affects sleep and quality of life, increases the use of healthcare resources, and is associated with
an increased risk for skin infections as well as comorbidities such as anxiety, depression, and attention deficit hyperactivity disorder.\textsuperscript{4-9} Timely intervention is therefore crucial, and dermatology nurses and nurse practitioners play a key role, particularly by counseling and educating patients and families.

**EPIDEMIOLOGY OF AD**

AD can occur at any age, although it usually starts in early childhood, with symptoms most frequently beginning to appear by 6 months of age. In the United States, the pediatric prevalence of AD in the general population is approximately 13%, with a somewhat higher prevalence among females compared with males.\textsuperscript{10} Among adults, prevalence is approximately 5-10\% and may represent either chronic or new-onset disease.\textsuperscript{9,11,12} While lesions in children are often widespread on the body, those in adults tend to be more limited.\textsuperscript{12}

Although AD affects all races and ethnicities, its prevalence is highest among Blacks, multiracial individuals, and individuals living in metropolitan areas.\textsuperscript{9,10,13} In one recent large U.S. study, self-identified Blacks had a greater than two-fold higher odds of AD compared with self-identified non-Hispanic Whites.\textsuperscript{14} Genetic factors did not explain this finding, suggesting that environmental factors were at play.

AD is becoming increasingly common — its prevalence among U.S. children and adolescents rose by nearly 50\% between 2000 and 2018. Prevalence is also rising in many other Western countries.\textsuperscript{12,15} While the reasons for this increase are unclear, possible explanations include changes in skin care practices, shifts in seasonality and climate, and migration to urban areas where environmental risk factors are more prevalent.\textsuperscript{16}

**GENETIC DRIVERS OF DISEASE**

**FAMILY HISTORY**

Several studies have confirmed that a family history of AD increases the likelihood that a child will be diagnosed with the condition.\textsuperscript{17,19} In one recent large study, a parental history of AD was associated with a threefold increase in the odds of developing AD among children.\textsuperscript{20} In another large study from Sweden, AD prevalence in young children (0-4 years old) was 27\% when neither parent had AD, 38\% when one parent was affected, and 50\% when both parents

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were affected. Maternal and paternal family history have a similar effect on risk. AD is also associated with a family history of other atopic diseases, including allergic asthma, allergic rhinitis, and allergic conjunctivitis.

### SPECIFIC GENE ASSOCIATIONS

The most robust known genetic risk factor for AD is loss-of-function mutations in *FLG*, the gene that encodes filaggrin, a protein found in the stratum corneum (cornified layer) of the epidermis that is essential to skin barrier function. Filaggrin, which binds and condenses keratin, is broken down into amino acids that help form natural moisturizing factor. This moderates skin pH, promotes skin hydration, and helps prevent infections. Individuals with and without AD who have loss-of-function *FLG* mutations have significantly increased water loss within their skin compared with individuals who lack these mutations.

Besides *FLG* loss-of-function mutations, studies have linked AD to alterations in at least 60 other genes related to skin inflammation, immunity, susceptibility to infections, and expression of immunoglobulin E (IgE). Some of the most robust evidence links AD to alterations in genes that regulate signaling by interleukins (IL) such as IL-4, IL-13, IL-5, and IL-12. Risk for AD is also moderately to strongly linked to mutations in *DOCK8, STAT3, DEFB1*, and *PGM3*, which function in immunologic host defense, and in *CARD11*, which encodes a scaffolding protein that helps regulate lymphocyte receptor signaling.

Studies of patients with AD have identified alterations in genes encoding pro-inflammatory and immune-related molecules such as IL-4, interleukin 4 receptor alpha (IL-4RA), IL-13, cluster of differentiation 14 (CD14), and others. These findings underscore the role of systemic inflammation in AD.

Genetic patterns of AD vary by race and ethnicity. Loss-of-function mutations in *FLG* have been identified in approximately 30-50% of White patients with AD, but among non-White patients, prevalence and specific gene loci vary substantially. For example, in studies using whole-genome sequencing and genetic risk scores, gene variants linked to AD in Whites were not associated with AD in Blacks, suggesting that the expression of genes involved in skin barrier function and immunity may differ. Given that AD in the United States is most prevalent among Blacks, it is key to better understand genetic drivers of disease in these patients.

### FIGURE 2 Pathophysiology of Atopic Dermatitis

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>SKIN TRIGGERS</th>
<th>DISEASE STATE</th>
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<tr>
<td><strong>Genetic Susceptibility</strong>&lt;br&gt;• FLG and other mutations</td>
<td>Sweat&lt;br&gt;Irritants&lt;br&gt;Pruritogens&lt;br&gt;Stress</td>
<td>• Dry Skin&lt;br&gt;• Lichenification</td>
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<td><strong>Environmental factors</strong>&lt;br&gt;• Allergens&lt;br&gt;• Pollutants&lt;br&gt;• Temperature and climate&lt;br&gt;• Diet&lt;br&gt;• Antibiotics&lt;br&gt;• In utero exposures</td>
<td><strong>Acute Flares</strong>&lt;br&gt;• Rash and pruritus&lt;br&gt;• Excoriations</td>
<td><strong>Complications and comorbidities</strong>&lt;br&gt;• Skin infections&lt;br&gt;• Atopic march: Food allergies, rhinitis, asthma</td>
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Studies in Asia have also identified gene variants among patients with AD that have not been strongly linked to disease in Whites, underscoring the genetic complexity of AD. This also suggests that the relative importance of filaggrin, inflammation, allergy, and microbial dysbiosis may vary from patient to patient.21,23 This is a growing area of research aimed at personalizing medicine, improving treatment selection, and optimizing therapeutic outcomes.

**SKIN BARRIER DISRUPTION**

Disruption of the epidermal barrier is a universal feature of AD that is key to its pathophysiology. Patients with AD have defects in the terminal differentiation of keratinocytes in the epidermis, as well as decreased expression of claudin-1, a protein that helps form tight junctions between cells in the skin’s granular layer.21 These abnormalities predispose patients to increased transepidermal water loss, leading to xerosis, pruritus (itch), excoriations (scratches), and penetration of the skin by allergens and microbes, leading to allergic sensitization and increased susceptibility to infection.29 Patients with low filaggrin levels are especially prone to dry skin due to reduced levels of natural moisturizing factor in the stratum corneum.

Thus far, however, it is unclear whether epidermal barrier dysfunction in AD precedes immune dysregulation and inflammation, or whether AD starts with immune dysregulation, which then causes skin barrier disruption. Two competing theories capture this debate. The “inside-out” theory states that the pathophysiology of AD begins with epidermal inflammation, particularly the overexpression of type 2 immune pathways, which leads to disruption of the skin barrier.21,25 The inside-out theory is primarily supported by research showing that inflammation in AD weakens the skin barrier by decreasing filaggrin production in the stratum corneum.

In contrast, the “outside-in” theory proposes that AD starts with skin barrier disruption, which then leads to allergic sensitization and inflammation. The outside-in theory is mainly supported by studies linking AD to FLG loss-of-function mutations.30,31 (Note that patients with AD who have low cutaneous expression of filaggrin tend to have earlier-onset and more chronic disease than patients whose skin has higher levels of filaggrin.)21,30,32,33 In addition, mice with filaggrin deficiency have been shown to experience passive transfer of allergens into the skin, and keratinocytes from mice with knockdown of FLG absorb heavy metal tracers and fluorescent dyes.

These competing theories remain under active debate. Future studies may better clarify their role in AD overall, as well as in specific patient populations and disease subtypes. In both theories, however, immune activation, alterations in the skin microbiome, and environmental factors are crucial to the pathophysiology of AD. We will discuss each in turn in the following sections.

**IMMUNE DYSREGULATION**

When the epidermis is exposed to allergens, keratinocytes initiate an initial immune response that leads to an increase in nonspecific immunoglobulin E (IgE). If allergen exposure persists, specific, allergen-targeted IgE increases. This type 2 immune response is the primary immunologic pathway in AD.34

In this pathway, exposure to allergens causes dendritic cells in the skin to migrate to nearby lymph nodes, where they activate T helper 2 (Th2) cells, leading to the upregulation of proinflammatory cytokines such as IL-4, IL-13, IL-5, IL-31, and CCL18. The end result is the downregulation of terminal differentiation genes and tight junction products, which worsens skin barrier dysfunction.35

Studies indicate that IL-4 and IL-13 play an especially important role in patients with AD, as these cytokines are highly increased in the skin of patients with both acute and chronic disease.34 IL-4 reduces the expression of genes involved in maintaining the skin barrier, and both IL-4 and IL-13 significantly reduce the production of filaggrin by keratinocytes, even among patients who do not have FLG mutations.

In addition to Th2 activation, the dysregulation of other T helper cells and cytokine pathways (e.g., Th22, Th17/IL-23, and Th1) also contributes to skin barrier dysfunction in AD, particularly in some disease subtypes.34 Other types of immune cells also play a role, including cytotoxic T cells, innate lymphoid cells, eosinophils, mast cells, and B cells.

**MICROBIAL DYSBIOSIS**

In healthy individuals, the skin microbiome (a diverse mixture of bacteria, fungi, and viruses) helps support the normal skin barrier and protects against inflammation and infection. This is largely because microbiota produce bioactive molecules that inhibit pathogen invasion.36 In patients with AD, decreased amounts of lipids in the skin lower the production of antimicrobial peptides, which can lead to microbial dysbiosis. This is characterized by reduced microbial diversity in the skin and increased colonization by potential pathogens, which can alter the immunologic response of the host and thereby reduce natural antimicrobial activity within the skin.

Patients with AD are significantly more likely to be colonized by the bacterium *Staphylococcus aureus* compared with individuals without AD. In a recent analysis of 95 studies involving patients with AD, *S. aureus* was cultured from...
70% of lesional skin sites compared with 39% of non-lesional sites. In addition, patients with AD had a nearly 20-fold higher odds of *S. aureus* colonization compared with healthy controls.

Microbes found on skin can be difficult to culture. As a result, advances in molecular testing methods have led to more detailed studies of microbial dysbiosis. A recent meta-analysis of studies using these “culture-free” methods confirmed that patients with AD had a greater skin prevalence of *S. aureus* and less overall bacterial diversity, especially on skin lesions.

*Malassezia*, the most common fungi found on healthy human skin, tends to be less abundant on the skin of patients with AD, who instead have a greater diversity of other fungal species. Patients with AD can actually develop allergic sensitization to *Malassezia*, leading to greater production of specific IgE antibodies and the upregulation of proinflammatory cytokines. Such sensitization may play an important role in AD pathology for some patients.

The results of these studies highlight how microbial dysbiosis of the skin may be associated with alterations in the immune response in AD. Flares in AD are often associated with microbial dysbiosis, while successful treatment of AD appears to improve the diversity of the skin microbiome, suggesting that dysbiosis is not just a feature of AD, but a possible contributor to AD onset and chronicity.

### ENVIRONMENTAL FACTORS

Many environmental factors can also increase AD risk and trigger disease flares. In indoor environments, these factors include allergens (e.g., nickel, rubber, and fragrances), and airborne pollutants (e.g., tobacco smoke and volatile organic compounds). A well-documented outdoor risk factor is exposure to air pollution, particularly the many pollutants found in vehicle exhaust. Controlled studies have documented higher rates of AD among individuals who live in areas with higher airborne concentrations of these pollutants. Numerous other environmental risk factors have also been implicated (Table 1).

For patients with established disease, common triggers of symptom flares include stress, low humidity (which increases transepidermal water loss and xerosis), exposure to irritating or itch-inducing fabrics and skin products, and the use of soaps and detergents that increase the pH of the stratum corneum and promote transepidermal water loss, irritation, pruritus, and excoriation. Research indicates that soaps and detergents decrease natural moisturizing factor and impair the skin barrier more among patients with AD than healthy controls. Temperature is also important: Sweating can contribute to skin irritation and flares. In the hottest areas of the United States, for example, outpatient
The Atopic March

The term “atopic march” describes the natural history and progression of atopy during infancy and childhood, starting with AD and food allergy and progressing in later childhood to asthma and allergic rhinitis. For example, a child might begin to show signs of AD at 2 months of age, food allergy at 1 year of age, and allergic rhinitis and asthma in subsequent years during early childhood. The concept of the atopic march not only describes the onset of allergic diseases in an individual patient, but also the most common ages of onset of these conditions on a population level. Note that symptoms related to AD most often begin by 6 months of age, while food allergy, asthma, and allergic rhinitis are more likely to develop later in childhood (Figure 3).

Studies in both humans and animals support the concept of the atopic march. Individuals with loss-of-function mutations in FLG are at heightened risk for AD and other atopic diseases associated with Th2 inflammation such as contact allergy, allergic rhinitis, food allergies, and asthma. In a widely cited study of mice, localized skin inflammation in response to skin exposure to ovalbumin (chicken egg allergen) was associated with reactive airway symptoms when the mice were later exposed to the same allergen in aerosolized form. The mice also showed biological changes that are typical of AD (increases in Th2 cytokines and allergen-specific IgE) and allergic rhinitis (nasal mucus secretion and eosinophilic infiltration).

Studies indicate that IgE plays an important role in the atopic march. Among patients with AD, a high serum level of allergen-specific IgE (found in about 80% of patients) is associated with an increased likelihood for developing food allergy, allergic rhinitis, and asthma. Higher levels of IgE are associated with earlier-onset and more severe AD, and it has been estimated that up to 60-70% of individuals with severe AD subsequently develop asthma compared with only 20-30% of patients with mild AD and less than 10% of the general population.

It is important to note that the atopic march does not occur in all children with AD. In one recent large study of children with a historical AD diagnosis, researchers examined the onset and timing of several symptoms of atopy, including itchy rash, wheeze (asthma), and sneezing or runny nose (allergic rhinitis). The most common ages of symptom onset followed the atopic march pattern: Itchy rash started earliest in life, followed by wheeze and rhinitis symptoms. Nonetheless, eight distinct patterns of atopy were identified, the most common being no current symptoms (51% of participants), followed by active AD without rhinitis or wheeze (15%). Only 3.1% of children showed the typical atopic march pattern in which AD preceded wheeze and allergic rhinitis (the study did not examine food allergies).

Thus, it is important for clinicians, patients, and families to understand that while AD (particularly earlier-onset and more severe disease) is associated with an increased risk for the subsequent development of other allergic diseases, this type of progression may not occur and cannot be predicted with certainty for any individual child.

Conversely, studies indicate that some environmental factors help protect against AD. Examples are ultraviolet (UV) light, consumption of fruits and vegetables, in utero exposure to long-chain omega-3 fatty acids and probiotics, and exposure early in life to certain bacteria, viruses, and parasites, which may support the normal development of the immune system (the so-called “hygiene hypothesis”). Interestingly, early-life exposure to antibiotics is associated with increased risk for developing AD, which may lend further support to the hygiene hypothesis.

TREATMENT PATHWAYS IN ATOPIC DERMATITIS

Treatment goals in AD are to reduce or eliminate symptoms and achieve long-term disease control. Many patients can reach these goals by avoiding triggers and combining nonpharmacologic interventions with topical therapies. For those with more severe AD, systemic treatments may be needed.
"Atopic dermatitis is a common, relapsing inflammatory disease in which genetic and environmental factors, immune activation, skin barrier disruption, and microbial dysbiosis all interact to cause symptom onset and subsequent flares."

NONPHARMACOLOGIC INTERVENTIONS

The regular use of moisturizers improves skin hydration and decreases itch, redness, fissuring, and lichenification. This may reduce inflammation and lessen the need for prescription pharmacologic treatment in patients with AD. Moisturizers combine emollients that soften and lubricate the skin, humectants that attract and hold water, and occlusive agents that create a layer to impede water loss. For patients with AD, moisturizers should be hypoallergenic and fragrance-free, and are most effective if applied immediately after bathing or showering when the skin is as hydrated as possible.

Wet-wrap therapy can also be used to reduce inflammation. In this technique, a topical moisturizer is applied to lesional skin and covered with a wet layer of tubular gauze or bandage, followed by an outer dry layer. Additional nonpharmacologic interventions including taking frequent (up to once daily) short baths or showers with warm (not hot) water, and using non-soap cleansers that are fragrance-free, hypoallergenic, and have a neutral pH.

TOPICAL TREATMENT

Topical corticosteroids (either prescription or over the counter) are a mainstay first-line treatment for patients with AD who have responded inadequately to nonpharmacologic interventions. Corticosteroids act on T cells, monocytes, macrophages, and dendritic cells to interfere with antigen response and reduce secretion of proinflammatory cytokines. In clinical trials, topical corticosteroids decreased AD signs (such as redness and lichenification) as well as both acute and chronic pruritus. Given the lack of head-to-head studies of topical corticosteroids, choice of a specific agent is typically based on availability, cost, and patient preference. Selecting the lowest potency topical steroid that controls symptoms and that the patient will be willing to use is key.

Topical calcineurin inhibitors (tacrolimus, pimecrolimus) block T-cell activation to suppress the production of proinflammatory cytokines and also help control mast cell activation. Their intermittent use as maintenance therapy has been found to be more effective than use of moisturizers alone. Both tacrolimus and pimecrolimus are approved by the U.S. Food and Drug Administration (FDA) for the treatment of mild-to-moderate AD in non-immunocompromised adults and children aged 2 years and older. They tend to be used as second-line therapy in patients with AD who are refractory to topical corticosteroids, or if patients develop skin atrophy. Both tacrolimus and pimecrolimus have FDA black box warnings for malignancies, although these have been reported rarely and a causal link has not been established.

Phototherapy with UV radiation targets inflammatory cells in the skin, which can inhibit T-cell infiltration, cytokine production, and the activity of antigen-presenting cells. Phototherapy can be a good option for patients whose AD is refractory to topical treatments and nonpharmacologic interventions. Narrowband, ultraviolet B light is used most frequently due to its relative safety, but other forms of phototherapy are also available. Dosing is based on skin type. Phototherapy can be used alone or in combination with systemic treatments. For safety reasons, phototherapy always should be administered by an experienced clinician.

CONVENTIONAL SYSTEMIC TREATMENTS

For patients whose AD is inadequately controlled by topical treatments and phototherapy, clinicians may consider prescribing an oral immunosuppressant, most commonly cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil. Note that although these drugs have shown efficacy in retrospective studies and clinical trials, their use in the treatment of AD is off-label. In addition, due to their immunosuppressive effects, these treatments are not generally recommended for long-term use. Finally, because only a few studies have compared these agents directly in AD, it is unclear which immunosuppressant drug is most effective.

Methotrexate is an oral antifolate metabolite. Because it inhibits DNA and RNA synthesis, it shows preferential effects on rapidly dividing cells, including T cells during inflammation. In studies of patients with moderate-to-severe AD, methotrexate was well tolerated and improved symptoms and quality of life.

Azathioprine also inhibits DNA synthesis. In a head-to-head trial comparing this oral purine analog with methotrexate in adults with AD, each drug exhibited...
comparable safety and tolerability, and led to similar improvements in an objective measure of AD severity.\textsuperscript{56}

Cyclosporine is an oral immunosuppressive drug that broadly targets T cells, thereby inhibiting the Th2 response.\textsuperscript{24} Among patients with AD, clinical responses to cyclosporine therapy tend to occur within 2-6 weeks.\textsuperscript{53}

Finally, oral mycophenolate mofetil hinders purine synthesis, which selectively affects T (and B) cells because they do not have a mechanism to scavenge existing purine.\textsuperscript{53} A recent review of patients with AD who received mycophenolate mofetil reported promising efficacy but also noted an increase in certain infections with longer-term use.\textsuperscript{57}

**NOVEL AND INVESTIGATIONAL AGENTS**

Our expanding understanding of the immunopathology of AD has facilitated studies of several targeted topical and systemic treatments that can reduce immune dysregulation.\textsuperscript{58} These include phosphodiesterase 4 (PDE4) inhibitors, Janus kinase inhibitors, and monoclonal antibodies. This is a rapidly growing area of research.

Phosphodiesterase 4, which hydrolyzes cyclic AMP (cAMP), helps regulate cell-mediated immunity. Immune cells from patients with AD show above-normal levels of PDE4 activity and decreased levels of cAMP.\textsuperscript{59} Small-molecule inhibitors of PDE4 have shown promise in treating AD and other inflammatory conditions. The topical PDE4 inhibitor crisaborole is approved in the United States for the treatment of mild-to-moderate AD in patients aged 3 months and older.\textsuperscript{60} Other PDE4 inhibitors, such as topical roflumilast and difamilast, are in late-phase development for use in patients with AD.\textsuperscript{61}

Targeted antibodies also show promise in patients with AD. The fully human monoclonal antibody dupilumab, which is approved for the treatment of moderate-to-severe AD in patients ages 6 years and older, blocks the synergistic effects of IL-4 and IL-13, thereby decreasing Th2 activation and IgE production.\textsuperscript{58,62} Dupilumab is administered subcutaneously.

A number of other antibodies that target interleukins are being studied in AD, such as lebrikizumab, tralokinumab, and nemolizumab. The monoclonal antibody omalizumab has a slightly different mechanism of action: it directly binds IgE, which decreases mast cell degranulation and inhibits release of inflammatory mediators.\textsuperscript{63} In a recent study of children with severe AD, subcutaneous omalizumab significantly outperformed placebo and decreased the need for topical corticosteroids.\textsuperscript{64}

Proinflammatory pathways in AD often involve Janus kinase (JAK).\textsuperscript{65} Tofacitinib is a small-molecule JAK inhibitor that blocks Th2 cytokine signaling. In a recent double-blind placebo-controlled phase 2 study, topical tofacitinib significantly improved disease scores among adults with AD.\textsuperscript{66} Topical ruxolitinib, another JAK inhibitor, became the newest addition to the AD armamentarium, approved by the FDA in August 2021 for the short-term and noncontinuous chronic treatment of mild-to-moderate AD in nonimmunocompromised patients 12 years and older whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable. Oral abrocitinib is another JAK inhibitor currently under FDA review at the time of this writing.\textsuperscript{65}

Much more information on these targeted topical and systemic agents will be included in forthcoming issues of *Dermatology Nurse Practice*. **SUMMARY**

AD is a common, relapsing inflammatory disease in which genetic and environmental factors, immune activation, skin barrier disruption, and microbial dysbiosis all interact to cause symptom onset and subsequent flares. AD can occur at any age but most commonly begins during infancy or early childhood. Rapid intervention is important to avoid or mitigate sequelae, including sleep disruptions, reduced quality of life, skin infections, and comorbidities. Nonpharmacologic interventions involve the reduction and/or elimination of triggers and use of moisturizers to improve the integrity of the skin barrier. Pharmacologic treatment is based on controlling inflammation, primarily by reducing T-cell activity. Conventional topical therapies include corticosteroids and calcineurin inhibitors, along with phototherapy. Several established oral immunomodulators are used off-label for patients with AD who do not respond to topical treatment. Novel and investigational therapies include monoclonal antibodies and small molecules targeting various components of inflammatory pathways. These have shown promise for the later-line treatments of refractory AD and are an active area of research.
REFERENCES


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REFERENCES (continued)


Caring for toddlers and young children with atopic dermatitis (AD) can be challenging for a variety of unique reasons. Specific barriers to effective management include complex routines, fear of medications and their side effects, and cooperation of the child and acceptance of treatments. Parents also struggle searching for causes and treatments of their child’s condition. They often are looking for the “one trigger or cause” that their child can avoid to magically make things better. Unfortunately, the management of AD is rarely that simple.

While quality of life challenges in toddlers and young children will vary depending on the individual patient, they usually center on the following constellation of issues:

• Distressing, unrelenting itch
• Patient and family sleep disruption
• Impact on behavior and mood
• Impact on growth and development
• Impact on parent-child relationship

For many young patients and their families, there is confusion about which medications to use, where topicals should be applied, how much topical medication should be applied (and how often), as well as what should trigger a “step up” or “step down” in care. Parents often fear the side effects of various medications—especially corticosteroids—and are particularly sensitive to black box warnings. Everyone is frustrated with the chronic nature of the disease. Parents will often tell me that “I used the medication, but my child didn’t get any better.”

Patient education is paramount for parents of toddlers and young children to help them understand that AD
"Offer developmentally appropriate expectations for the child based on their age and level of maturity instead of simply casting all responsibilities onto mom and dad. This is a partnership of the entire team."

is an inflammatory, chronic skin disease. And this can’t just be education at the first visit—it needs to be reinforced often, especially when families and kids come in looking worn down and frustrated. These are some of the points that I generally try to emphasize:

- Keep your child’s skin hydrated
- Focus on decreasing inflammation and controlling itching
- Keep the skin intact to prevent infection
- Eliminate known triggers

I find it helpful to provide families with a written “action plan” that includes guidance on bathing/skin cleansers, moisturizers, appropriate use of topical medications, application of wet wraps or zinc oxide wraps, and control of itching/infection. Giving patients an at-home reference tool is crucial—to expect families to remember even half of what you tell them in the office is likely unrealistic. You’ll want families to understand the difference between “irritants” and “allergens” and encourage them to have their child avoid known allergens.

Give the family strategies for interrupting the itch-scratch cycle. Foster a supportive team approach that doesn’t cast blame on certain individuals or external triggers of itching and scratching. Focus on what the child CAN do to bring relief and control instead of hand wringing over all of the things he/she CAN’T do. Normalize stress as a trigger and help the child develop coping strategies. Teach relaxation strategies to help refocus the child’s attention on positive qualities.

Every patient and their family will have a different level of sophistication regarding their grasp of medical terms and concepts. This requires providers to meet our patients and families where they are and exchange information prudently to ensure understanding of the patient and family preferences, potential treatment barriers, and goals of therapy. Proactive problem solving is key—do what you can to anticipate issues before the patient leaves the office. Are financial issues a concern? How might school and work get in the way of medication regimens? Offer developmentally appropriate expectations for the child based on their age and level of maturity instead of simply casting all responsibilities onto mom and dad. This is a partnership of the entire team.

This all may sound like a lot to be mindful of, but trust me, it becomes easier with experience.

Let’s look at how this works in actual practice.

Shane is a 20-month-old toddler who came to our specialty pediatric practice about 14 months ago after being seen by various allergists and dermatologists in the community. He had been diagnosed with moderate-to-severe AD and was clearly extremely itchy and irritable. Shane’s parents told us that he slept only a few hours a night due to the intense
itchiness. He was significantly underweight, perhaps because of all of the energy he was expending scratching all the time.

Upon physical exam, we identified eczema on his scalp, face, neck, chest, back, arms, hands, legs, and feet. His parents told us that they bathed Shane twice a week for approximately 5 minutes at a time. His topical regimen included moisturizer once a day applied to his whole body and over-the-counter hydrocortisone to the worst lesions as needed. When I asked about other options such as topical steroids and wet wraps, I felt the presence of “Dr. Google” enter the room. I was faced with the usual reticence about the use of corticosteroids in children—which we all hear frequently—but was thrown somewhat of a curveball when his mother told me that she had heard wet wraps might cause their son to “catch cold.” It took some time and patience to parse through these issues and address the concerns of Shane’s parents.

As our team observed Shane at this initial visit, we began to suspect developmental issues due to his AD. He did not engage with us or any stimuli in our office at all, focusing solely on scratching. His mother informed us that he had not played with his toys for several weeks. This was rather alarming as it indicated that something needed to be done for this poor child, and soon.

I spoke to Shane’s parents about their son’s current treatment regimen and the impact his AD was having on his development. We reviewed the pathophysiology of AD in a simplified manner, using bricks and mortar to represent the skin barrier and the holes that appear without rigorous attention. Fortunately, Shane’s parents agreed to a simple yet more aggressive treatment plan that included a daily bath, mid-potency topical steroids, frequent moisturization, and wet wraps. I felt comfortable at the end of the visit that the education I provided was going to be enough to promote adherence to our agreed-upon strategies. To help reinforce the messaging, I provided Shane’s family with educational materials and an action plan to take home with them.

Shane was back 3 weeks later for his initial follow-up visit. His demeanor had improved exponentially. He was developmentally appropriate and engaged with our staff and his surroundings. His parents said they were following our treatment plan, and the results were significant as Shane’s skin was mostly clear. Nevertheless, his mom expressed concerns that Shane’s AD was “coming back” since she felt he looked better a few days ago than he did at this visit. We reiterated to her one of our messages from our initial visit—AD is not a disease with a straight line of improvement but rather a chronic disease with ebbs and flows that require ongoing maintenance. We reviewed our written action plan and emphasized the need to stick with things even when things didn’t visibly appear to be getting better.

We’ve now been seeing Shane every 3 months for about the last year. Subsequent visits have been much smoother—his family seems to “get it” and is able to manage his daily maintenance and flares confidently. Shane is sleeping through the night, growing, and gaining weight.

We all know that parents of toddlers and young children are often overwhelmed, even when their children are completely healthy. Throw AD into the mix, and the dynamic throws some families into a tailspin. It’s incumbent upon providers to give patients and their families the support they need to get past the more challenging barriers while also being realistic that they can’t let their guard down just because things seem to be getting better.
In an increasingly connected world, influences abound. How many of us have spent hours explaining to patients that what they read online simply isn’t true (yes, I see you all raising your hands) and undoing the misinformation they bring into our practice?

Yet at the same time, outside influences can sometimes unexpectedly make our jobs easier and break through the defenses of some of our more stubborn patients. Whether it’s a connection to a formal network of patients or simply a random encounter on the street, you never know what’s going to make the difference.

When I first met Kristi, she was a shy 13-year-old with a history of pruritus and neurotic excoriation. She was referred to us by her primary care provider for evaluation of skin symptoms that had been getting progressively worse over the last several months. At our initial meeting, Kristi told us that she had had dry, sensitive skin “for as long as I can remember,” but that lately she was unable to sleep well at night, often waking up to blood on her sheets. She had already been told by several previous providers that she had mild atopic dermatitis (AD), which had always been treated conservatively with basic skin care regimens and moisturizers.

Upon clinical exam, Kristi had numerous erythematous patches and plaques with secondary excoriations on her arms, legs, and scattered areas of her back. She expressed frustration that the moisturizers she was using along with her avoidance of skin cleansers, perfumes, and fragranced products was not controlling her condition (“I’m doing everything they told me to do” she said).

By this time, Kristi already had clinical signs of chronic skin changes. Common features of chronicity, including lichenification (thickening of the skin) and hyperpigmentation of the skin were readily apparent. 

**Finding An Unexpected Ally**

by Keischa Cash, DNP, APRN, DCNP, FNP-BC

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This made her feel noticeably uncomfortable as I watched her try to cover her arms and legs each time that I moved the gown to examine her skin.

Over the next 6 months, we began our journey of trying to help Kristi manage her skin symptoms. I tried anything and everything that I thought might help—oral antihistamines for her seasonal allergy symptoms, topical emollients and humectants, topical and oral antibiotics, oral and topical corticosteroids, topical calcineurin inhibitors, and even phototherapy with excimer 2-3 times weekly. Her skin disease was recalcitrant to everything we tried. Nothing worked. Even worse, Kristi was becoming more detached at home and school because she was embarrassed of her appearance. She was afraid to show her arms and legs because of the scars caused by clawing and digging at herself. She began wearing clothes that completely covered her arms and legs. Yes, that meant sweatshirts even in the scorching south Florida heat and humidity.

Sixteen months after I first saw Kristi, I decided it was time to introduce the possibility of taking dupilumab to help with her AD. The efficacy and safety data were the easy sell. The hard part was convincing Kristi to take an injectable medication. She was terrified of needles. Her mom told me horror stories of prior visits to the pediatrician as a young girl when Kristi would basically need to be forcefully held down in tears to get the childhood vaccines she needed. Every year was the same fight over the flu shots, which Kristi usually won. “She just wears me down,” her mom told me.

When I heard these stories, I knew it was going to be a battle to overcome Kristi’s fears of injections, especially since she would need these every 2 weeks for the foreseeable future. While I was ready to start Kristi on dupilumab right away with some samples I had in my office, Kristi and her mom said they would need time to think about it. I wasn’t terribly optimistic.

Fortunately, as is sometimes the case, an unexpected ally was out there waiting to help. One of Kristi’s neighbors, Valerie, was a teenager who lived a few blocks away. While they weren’t particularly close, Kristi knew that Valerie also had skin issues as an adolescent. They ran into each other a few days after Kristi’s latest appointment in my office, and Kristi

"...outside influences can sometimes unexpectedly make our jobs easier and break through the defenses of some of our more stubborn patients."
noticed how great Valerie’s skin looked. Valerie told her how dupilumab had changed her life. She had apparently been having a horrible time with her AD, but since starting on dupilumab, her skin was nearly clear for the first time in years, and she was no longer itchy all the time. Valerie was also apprehensive about needles, but she assured Kristi that she would quickly get over her fears once she realized how much better she felt and how much more confident she would become with dupilumab.

This was apparently all that was needed to convince Kristi to give dupilumab a try. She came back to my office and, while still a bit skittish, gritted her teeth while I gave her the first two subcutaneous injections—one in each arm. Fortunately, her insurance company approved Kristi’s use of dupilumab so it seemed like it was smooth sailing.

Because of her fear of the injection, I continued to have Kristi and her mom come to the office to receive her injections for the first few months until they felt confident enough administering the medication on their own. Before sending them off, I showed them how and where to administer dupilumab during multiple visits, wanting to reinforce the procedure and answer any questions they had. They were instructed, as all of our patients are, to call if there were any problems.

It’s now been 2 months since Kristi began self-administering dupilumab. Things are going well—no issues with the self-injections—and Kristi’s condition is progressively improved. Her skin is slowly but surely clearing, and she now feels confident enough to wear short-sleeved shirts and shorts while thankfully ditching those bulky sweatshirts. Kristi has even mentioned to me that she’s now motivated to try to improve her diet and lose some weight, which is another thing I find often happen in patients with AD. Once their skin gets better, it no longer has to be their sole focus, and they can begin working on other aspects of a healthy lifestyle that they had been ignoring.

I have never met Valerie and know her only through the stories that Kristi and her mom have told me, but I say a silent “thank you” to her every time Kristi tells me about all of the positive things happening in her life. She was truly a most unexpected, but welcome, ally.
The “Complicated” World of the Teenaged Patient

by Megan Lewis, MSN, RN, CPNP-PC

If you asked me to sum up my teenaged patients in one word, I wouldn’t hesitate to find an answer. Complicated.

Working in pediatrics, we see kids of all ages, many of whom have really challenging physical manifestations and complications to overcome. But as puberty hits and the psychological stakes for our patients are raised ever higher as they reach their teenaged years, the difficulties become, well, they become a lot. There is perhaps nothing as emotionally draining for the pediatric provider as dealing with teenaged angst.

Let me give you an example. I first met Charlotte when she was 12 years old. She had just recovered from an extremely serious asthma exacerbation that required an airlift and ICU admission at our hospital. She fortunately recovered, but by the time I met her, both Charlotte and her mother were overwhelmed by her myriad symptoms and nervous about the future. As with many patients who come to our practice, Charlotte had multiple atopic diseases. In addition to severe asthma, she had also been diagnosed with atopic dermatitis (AD) and various environmental allergies. At our initial meeting, Charlotte and her mom reeled off a long history of allergies, many of which were quite bothersome. Charlotte had been previously evaluated by an allergist for potential environmental triggers and tested positive for allergies to pet dander, dust mites, trees, grass, and weed pollens.

With the onset of puberty, both Charlotte and her mother told me that her allergies seemed worse than ever. They dreaded the approach of every spring and fall knowing the exacerbations that were likely to occur. Consequently, our initial appointments focused on Charlotte’s asthma and developing strategies to...
help her maintain healthy airways. We focused a great deal on her long list of environmental triggers, going through them one by one. There were already some excellent steps her family was taking—dust mite covers for bedding, taking most of the stuffed animals from Charlotte’s bedroom, closing the windows at night, turning on the air conditioner—but these only led to a mild improvement in some of Charlotte’s skin issues while doing nothing to alleviate any asthma or allergic rhinitis symptoms.

And that’s not all. Within a few months of our initial meeting, Charlotte developed a frustrating condition called pollen food syndrome, a condition characterized by an immediate allergic reaction in the lips, mouth, and throat. It is most often caused by certain kinds of raw fruits or vegetables. In Charlotte’s case, she developed an itchy throat and mouth in response to several fresh fruits that she previously enjoyed such as peaches, watermelon, and apples.

With all of this going on, we decided that Charlotte was a good candidate for allergy immunotherapy. Fortunately, this was effective and helped control her reaction to many of the allergens that had previously been problematic, including pollens, dust mites, and pet dander. Because Charlotte was in our office so frequently to receive her immunotherapy shots, we were able to regularly check on her AD as well.

We initially focused on basic management principles—a daily brief bath, use of mild soap, and moisturizer twice a day. Charlotte agreed to eliminate the fragrant products she had previously been using. Charlotte and her mother were hesitant to incorporate a topical steroid due to fear of skin pigment changes and potential side effects, but as things progressively became worse, Charlotte agreed to try hydrocortisone 2.5% ointment twice daily on her erythematous patches. This led to some minor improvements, though there were still regular outbreaks of lichenified plaques month after month. Following current stepwise AD guidelines, we added tacrolimus 0.03% daily as maintenance therapy and hydrocortisone valerate for treatment of persistent patches. Charlotte also incorporated wet wraps and weekly bleach baths into her regular routine. Adherence issues were a concern for a young teenaged girl, but studies have shown these would be the best treatment steps at this time.

While these changes kept things from getting worse, my concerns began to shift from management of Charlotte’s physical symptoms to her psychological ones. She was about to enter high school, which is always a sensitive time for our patients with moderate-to-severe AD, and you could tell that her skin issues were beginning to affect her mood and overall demeanor. Her AD had begun to shift from more easily hidden areas such as her chest, arms, and legs to more flexural areas, her face, and thighs. Perhaps most upsetting, Charlotte developed significant periorbital eczema with ocular pruritus and drainage (“It’s gross,” she told me). A pediatric ophthalmologist was brought in, who recommended eyelid hygiene, lash washes, and topical erythromycin for the lash borders.

Her asthma began to flare as well, with symptoms emerging many nights and during periods of even moderate exercise despite use of a daily inhaled steroid. We adjusted her regimen by shifting to a combination budesonide-formoterol formulation. Around her 15th birthday, Charlotte had an anaphylaxic episode after receiving her allergy shots, which required emergency epinephrine.

With her numerous issues and laundry list of recommendations to help manage everything, it was clear that Charlotte was beginning to feel overwhelmed. We reduced her immunotherapy regimen to a low maintenance dose to reduce the risk of shot reactions and AD flares. Charlotte admitted that even that adjustment didn’t really make much of a difference in

"As our patients age and their parents recede into a more supportive and less directive role, we have to learn how to adapt our conversations and give our teenaged patients the independence they are going to need to manage their chronic disease over the long term."
her skin response. “It’s all just too much to remember,” she told me. “I can’t do this. I have to do that. I just want to be normal!”

These are the kinds of things that are hard for a provider to hear. We want our patients to feel normal too, but some of them just have so many things going wrong simultaneously that it’s a challenge simply to keep them at a level of “tolerable” instead of “terrible.”

So we kept trying.

In her sophomore year of high school, Charlotte’s AD got worse in the heat of the summer and early fall, which we eventually were able to link to the polyester school and sports uniform she wore every day. In other words, contact dermatitis. We solved that problem by having her wear cotton bike shorts and a cotton shirt underneath her clothes to create a barrier. Charlotte wouldn’t even consider not wearing the same uniform as the rest of the kids—again, the wanting to be and look “normal.”

Over the next few years as she progressed through high school, Charlotte had her good and bad spells, like many of our patients do who have longstanding disease. She cycled through moderately high to medium potency topical steroids to help with her AD, both of which helped a little but not enough for us to think they would be a long-term solution. We tried to get Charlotte onto dupilumab, which was only approved for use in patients 18 years and older at the time, but despite multiple levels of appeals, her family’s insurance company denied its use.

With the frustrations mounting, I asked another specialist and colleague of mine to offer his input. He listened to Charlotte’s history, asked some pointed questions about her day-to-day routine, and was able to tease out a few crucial items. For starters, we found out that Charlotte was using scented candles and incense in her bedroom nearly every evening, and she sprayed scented fabric freshener over her bedding every night before going to sleep. Remarkably, when she put a halt to these routines, her skin improved significantly. By the time her senior prom and graduation came around, with routine maintenance using topical medications, her skin was largely clear. It was a small, yet important victory to raise Charlotte’s morale.

Over the next few months after she went away to college, Charlotte’s AD began to flare again likely due to her new surroundings over which she had less control. We were finally able to get her onto dupilumab once she turned 18, which she has tolerated well for the last 2 years. I obviously don’t see Charlotte as often as I used to since she is hundreds of miles away at an out-of-state university, but I still keep tabs on her from time to time. These patients who we see so frequently and commiserate with during their few highs and frequent lows almost become part of our family.

Patients like Charlotte have taught me a lot. I spent so much time with her as a teenager managing her medications and talking to her about possible irritants and environmental triggers, but I never asked specifically to find out about her use of incense and fabric refreshers. It’s now something that is on my radar screen whenever I am seeing a teen with AD.

As a pediatric nurse practitioner, I see my patients go through many changes, and it requires flexibility to partner with them to provide the best care. As our patients age and their parents recede into a more supportive and less directive role, we have to learn how to adapt our conversations and give our teenaged patients the independence they are going to need to manage their chronic disease over the long term. As I said at the start, it’s a complicated situation, but our teenaged patients need the same comprehensive care partnership we provide to everyone who comes through our doors, perhaps just focused on a few unique areas.

**REFERENCE**

Although many patients diagnosed with atopic dermatitis (AD) in early childhood effectively outgrow their disease, some are not as fortunate and have their disease follow them into adolescence and then into adulthood. Young adults heading into college often make decisions about where to go to school and what avenue to focus on academically based upon how they think their skin might react in a new environment. They may eventually even need to steer away from certain occupations due to disease considerations. As an adult, AD can significantly influence relationships, intimacy, and commitment as patients face a fear of acceptance or rejection based on the lack of understanding regarding the complexity and unpredictability of their condition.

As dermatology providers, we have all witnessed the impact that the severe and chronic nature of AD can have on virtually every aspect of our patients’ lives. It can be particularly devastating for those adults who were initially diagnosed in childhood or infancy and have never been awarded a reprieve, instead being forced to struggle with school, personal relationships, and work while trying their best to keep their AD at bay. Each stage of life has its own set of challenges as these patients do their best to built a “normal” life.

As a dermatology nurse practitioner and researcher, I have had the privilege of building long-lasting relationships with a variety of adult patients who have suffered with AD through most of their lives. My interactions with them highlight a variety of key points as I accompanied them through disease exacerbations, general complications, and the gamut of treatments.

Let’s start with Janet, a 72-year-old who was initially diagnosed with AD as a child, meaning she has suffered with the condition for more than six decades. Janet has participated in a variety of clinical trials during the course of her disease, many for drugs that turned out not to work but some that did. An identical twin,
Janet was subjected to the cruel fate of having severe, unrelenting AD while her sister has always had perfectly clear skin. Janet said she was constantly being compared to her twin sister throughout their lives and admitted to feelings of inferiority because of her severe erythema, inflammation, and excoriations. New acquaintances would constantly look at Janet and her sister together and ask, “What’s wrong with your skin?”

Janet gave up any hope of outgrowing her disease decades ago, and her sense of inferiority has spilled into her adult life. As Janet’s disease progressed in her 50s and 60s, it began affecting her hands as she developed painful fissures, edema, and inflammation. These issues have made it impossible for Janet to perform ordinary daily tasks. She also wrestles with frequent flares of eczema that affect her face and body. Having an impaired skin barrier provides easy access for pathogens and bacteria that can cause infection leading to exacerbation of her disease. Consequently, Janet’s vacations often begin with her identifying the location of the nearest hospital/emergency room in case of a staph infection or cellulitis. Not exactly the makings of a romantic trip with your spouse.

Another of the “normal” patients we regularly see in our practice is Ron, a 57-year-old who has fought for years to overcome chronic flares related to his AD. Although he long sought a healthy, happy relationship and wanted to get married, Ron has had difficulty maintaining a long-term relationship with women due to his unpredictable disease flares that make intimate situations difficult and awkward. That’s something we hear from a lot of our adult patients.

Earlier in his life, Ron’s AD was treated with far too many doses of systemic steroids by providers who did not understand the chronic nature of his disease. He would often report to the emergency room on weekends and holidays in a serious disease flare and would typically be treated with systemic steroids to provide immediate relief. The unfortunate result of this steroid overuse was the development of osteonecrosis of the hips. Over the course of last 5 years, I watched Ron deteriorate from needing a cane to help with ambulation to now being unable to ambulate freely. Today, he spends most of his waking hours confined to a wheelchair. Consequently, Ron now also frequently needs treatment for pressure sores that have developed on an already-impaired skin barrier. Nonetheless, he somehow remains upbeat, optimistic and cooperative—a testament to the human spirit and the ability to be hopeful in the face of adversity living with a chronic disease.

Nathan is the last “normal” patient I want to tell you about. He’s another of our patients with AD who has suffered with the condition for his entire adult life. At 43 years old, Nathan is slightly younger than Janet and Ron, and has benefitted much more from some of the newer treatment options that have become available in recent years. Nathan also has a younger sister with AD whose disease has followed a similar trajectory as his own, so at least he has had someone to commiserate with.

Nathan has been treated with the usual gamut of AD medications, including both cyclosporine and methotrexate, powerful and potentially effective immunosuppressants that each carry their own unique set of side effects. Nathan, however, is one of the lucky ones whose life has completely turned around with the introduction of dupilumab, the first biologic approved by the U.S. Food and Drug Administration for the treatment of AD. Although few adult patients see their disease totally clear on dupilumab, nearly all have complete resolution of pruritus, which typically has the biggest impact on sleep and activities of daily living. This benefit alone is a game changer for so many of our patients like Nathan, who is now able to enjoy life in a way he thought was long gone a few years ago.

Giving hope to our adult patients with AD, and especially those who have lived with the disease throughout their lives, is a constant challenge. Certainly the introduction of dupilumab, along with many of the biologic and novel topical agents currently under investigation, can be a powerful motivator. For so long, all we could offer our longest-suffering patients were drugs that, at best, could provide incremental, short-term benefit with unknown long-term side effects. My hope is that the “new normal” for many of our adult patients with AD will be a brighter future than they have ever known before.
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