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Atopic Dermatitis: Focusing on the Patient Care Strategy in the Managed Care Setting

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Atopic Dermatitis: Focusing on the Patient Care Strategy in the Managed Care Setting

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Intended Audience

Managed care pharmacists and pharmacy directors

Activity Overview

Atopic dermatitis (AD) is an inflammatory skin disease characterized by intense pruritus and age-related patterns of eczema. It typically begins before the second decade of life, has a relapsing clinical course, and is more common in adulthood than previously thought. But the impact of AD reaches far beyond the medical aspects of the disease itself. Data show that AD predisposes individuals to multiple comorbidities such as psychosocial issues, sleep disturbance, skin infections, and asthma. Due to its wide-ranging impact on patients' quality of life, the safe and appropriate use of evidence-based treatments of AD is paramount to prevent flares and limit morbidity. This article will address nonpharmacologic and pharmacologic interventions for AD and discuss how the pharmacist patient care process can be infused into daily practice to optimize patient health and medication outcomes.

Statement of Educational Need

Since the 1970s, the incidence of atopic dermatitis (AD) has increased by 2- to 3-fold in industrialized nations. AD is a chronic relapsing inflammatory skin disease that is associated with other atopic diseases and the most common skin disorder among children. AD impacts approximately 15% to 20% of children and 1% to 3% of adults worldwide. As a result, there is a significant economic burden felt by patients and their families and caregivers. In the last 40 years, there has been substantial progress with respect to understanding the pathogenesis of atopic dermatitis. These new insights related to the genetic, immunologic, and environmental impacts has paved the way for future novel treatments. Early diagnosis, patient education, self-management techniques, and treatment with existing and emerging drug therapies can reduce the unnecessary costs associated with AD and can improve clinical outcomes.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Explain the pathophysiology, signs and symptoms, and diagnostic criteria of atopic dermatitis (AD).
- Identify nonpharmacologic and pharmacologic options to manage AD, including guideline recommendations and emerging treatments.
- Examine managed care implications of AD treatment, including medical costs and resource utilization.
- Explore disease management opportunities for managed care pharmacists to improve the clinical and economic outcomes of AD.

Accreditation Statement

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OVERVIEW

This supplement to *The American Journal of Managed Care®* will address nonpharmacologic and pharmacologic interventions for atopic dermatitis and discuss how the pharmacist-patient care process can be infused into daily practice to optimize patient health and medication outcomes.

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REPORT

Overview of Atopic Dermatitis

Carmela Avena-Woods, BS Pharm, PharmD, BCGP

ABSTRACT

Atopic dermatitis (AD), also known as atopic eczema, is a chronic relapsing inflammatory skin condition. Incidence of AD has increased 2- to 3-fold in industrialized nations, impacting approximately 15% to 20% of children and 1% to 3% of adults worldwide. AD has a wide-ranging impact on a patient's quality of life and the burden from direct and indirect costs (approximately $37.7 billion in out-of-pocket costs) is shared by the families and caregivers of patients with AD. This article reviews the epidemiology, burden of disease, pathophysiology, and diagnostic criteria important for early diagnosis and treatment. New insights related to the genetic, immunologic, and environmental impacts of AD have created new treatment opportunities. Nonpharmacologic and pharmacologic interventions are discussed, with an emphasis on emerging treatments for AD. Healthcare providers play an important role in the management of AD to improve economic and clinical outcomes. Treatment strategies need to be individualized with a strong emphasis on patient education and self-management strategies to optimize outcomes and reduce unnecessary costs associated with the management of AD.

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For author information and disclosures, see end of text.

Atopic dermatitis (AD) is a multifaceted, chronic relapsing inflammatory skin disease that is commonly associated with other atopic manifestations such as food allergy, allergic rhinitis, and asthma.[1-3] It is the most common skin disease in children, affecting approximately 15% to 20% of children and 1% to 3% of adults.[4,5] Onset of disease is most common by 5 years of age, and early diagnosis and treatment are essential to avoid complications of AD and improve quality of life.[5] Individuals with AD were formerly referred to as individuals having eczema. However, the word "eczema" is a broad term that refers to various conditions causing inflammation of the skin. The purpose of this lesson is to review the epidemiology, burden of disease, pathophysiology, diagnostic criteria, and clinical presentation of AD to ensure that patients are correctly diagnosed and receive care in an appropriate and timely manner.

Epidemiology

Incidence of AD, also referred to as atopic eczema, has increased 2- to 3-fold in industrialized nations since the 1970s, with approximately 15% to 20% of children and 1% to 3% of adults affected worldwide.[4,5] Population-based studies in the United States suggest that prevalence is about 10.7% for children and 7.2% for adults.[6,7] Onset of disease commonly presents by 5 years of age, with the highest incidence occurring between the ages of 3 and 6 months, but it can occur at any age.[5,8] Approximately 60% of patients develop disease in the first year of life and 90% within the first 5 years of life.[5] Twenty percent of children who develop AD before 2 years of age will have persisting symptoms of disease; 17% will have intermittent symptoms by 7 years of age. Only 16.8% of adults with AD experience onset after adolescence.[9-11] AD commonly resolves by the time a child reaches adulthood; however, approximately 10% to 30% of patients will continue to have symptoms of disease.[12] A 2014 prospective cohort study of children with mild-to-moderate AD reported that, at any age, including up to 26 years of age, 80% of participants with ≥5 years of follow-up continued to have symptoms or had continued using medications for their AD.[13] Interestingly, investigators from the same cohort study identified that regardless of disease

severity, participants sought out their healthcare provider less frequently as they aged, suggesting that this may account for the common perception that AD resolves over time.[13] In contrast, a 2016 meta-analysis showed that only 20% of childhood AD persisted 8 years after onset and there was a median duration of 3 years for AD persistence.[14] Furthermore, AD was shown to be more persistent in males, in patients with late-onset disease, and in those with severe cases of the disease. Even with the inconsistencies among the above-mentioned studies, it is clear that AD is a chronic disease that is burdensome for many patients. A 2007 study further supports this claim, as an estimated 17.8 million persons, mostly undiagnosed, are living with AD in the United States.[8]

Burden of Atopic Dermatitis

Areas of disease burden most commonly impacted by AD include overall quality of life and the social, academic, and occupational realms.[3] The burden of AD is not limited to just the patient, because AD is a chronic relapsing skin disease that can persist into adulthood and burden of disease is frequently experienced by the patient's family. Several validated tools have been used to measure the adverse impact on quality of life during patient and family interviews, supporting a family-wide burden experience related to AD.[15-18] Similarly, patients, their families, and society bear a significant weight related to the direct and indirect medical costs associated with AD.[3,4,19,20] Direct costs include, but are not limited to, prescription and nonprescription costs, healthcare provider visits, hospital and emergency department visits, and hospitalizations. Indirect costs associated with AD include absenteeism from work, school, and physical activities; decreased productivity (presenteeism); and decreased quality of life (primarily due to sleep disturbance from itching, absenteeism, and time related to care).[21-24]

Quality of Life

Itching is the major symptom associated with impact on quality of life. For example, a US-based survey found 91% (n = 304) of patients with eczema experienced itching on a daily basis,[25] and 36% of patients identified decreasing the amount of itch to be their primary treatment goal.[26] Furthermore, itch has been associated with mental distress and increased risk for suicidal ideation in those with AD.[27] Of note, emotional stress has also been shown to increase itching, implying a bidirectional relationship.[28] Sleep disturbance is a frequent consequence of itching and is experienced by approximately two-thirds of patients with AD.[8,29] Patients with sleep disturbance report difficulty initiating and maintaining sleep, which leads to daytime fatigue.[30] Children with AD who experience sleep disturbances are associated with higher rates of developing attention-deficit/hyperactivity disorder, headaches, and short stature.[30-32] Sleep disturbances experienced by adults with AD are associated with poor overall health perception.[7] In addition to the physical symptoms, AD can lead to embarrassment from appearance, decreased self-esteem, and a negative impact on social life.[33,34] While a patient's quality of life is impacted tremendously, so, too, are the patient's parents and caregivers. An international study conducted in 2006 found that 30% of patients and caregivers believed other individuals in the household were impacted by AD.[34]

Economic Impact

A true economic impact of AD is difficult to measure due to the broad severity of AD disease and multiple cost contributors related to indirect and direct medical costs. A 2010 National Health Interview Study conducted in the United States estimated that 75% of people with eczema had visited a doctor at least once in the last year.[7] Furthermore, among those participating in this study, in the prior year, about 12% missed 1 to 2 days of work due to their eczema, and about 2% missed 3 or more days.[7] The current literature related to economic burden is very sparse, but a comprehensive investigation was conducted in the United States in 2006 by Bickers et al.[35] This study reviewed the financial impact of skin disease overall in the United States using various data sources (eg, surveys, databases, published literature) to estimate the costs of individual diseases.[35] The total burden of AD in Bickers et al was estimated at $4.228 billion (2004 USD) compared with psoriasis at $3.658 billion.[3,35] When converted to 2016 USD using the Consumer Price Index provided by the US Bureau of Labor Statistics, this equates to $5.37 billion (calculation: September 2004 consumer price index [CPI] = 189.9; September 2016 CPI = 241.428; costs in 2016 = $4.228 billion × [241.28/189.9] = $5.37 billion).[3,36] Direct costs were $1.009 billion, decreased productivity costs were $619 million, and costs due to decreased quality of life were $2.6 billion.[35] The costs reported in this study are very likely underestimated in the United States today, because while the prevalence estimate in the 2004 study was about 5%, today's prevalence is estimated at about 10.7%[6] (2011) in children and 7.2%[7] (2014) in adults. It is important to keep in mind that this study did not include nonprescription medication costs and decreased productivity beyond medical visits.[35] Finally, since this study was conducted almost 13 years ago, new research is required to adjust for new prevalence data, changing prescribing patterns, and additional contributing factors (eg, presenteeism) not accounted for previously.[3] A more recent study identified the average personal cost of AD in the month before an office visit (including direct and indirect costs) to be $274 per patient ($75 direct costs; $199 indirect costs).[37] This study also calculated a mean percentage of monthly available money spent on AD to be 34.8%, further supporting the high burden of disease experienced by patients with AD.[37]

Pathophysiology

Two major theories have been proposed to explain the cause of AD, the inside-out and outside-in hypotheses.[38] The inside-out hypothesis

proposes that allergic triggering leads to a weakened skin barrier that furthers allergen introduction and presentation.[38] This would suggest that inflammation is the culprit for an impaired skin barrier, leading to increased penetration of allergens and microbes causing a reaction. The outside-in hypothesis proposes that the impaired skin barrier precedes AD and is required for immune dysregulation to occur.[38] For example, the down-regulation of filaggrin (FLG), required for proper skin barrier function, could make the skin more susceptible to immune dysregulation and lead to AD. It is unlikely that the 2 theories are exclusive and both most likely play a role in the pathogenesis of AD, discussed further below.[38,39]

Risk Factors

There are 2 major risk factors for the development of AD: 1) genetic defect in the *FLG* gene[40] and 2) family history of atopic disease.[5] A family history of atopic disease is strongly correlated with AD, as approximately 70% of patients with AD are positive for this risk factor.[5,41] Risk of AD increases with the number of parents positive for atopic disease by 2- to 3-fold and 3- to 5-fold (1 and 2 parents, respectively).[5,42,43] In addition, a maternal history may be more predictive for AD.[44]

Concordance rate studies for atopic dermatitis are higher among monozygotic twins compared with dizygotic twins (approximately 80% and approximately 20%, respectively).[1,45,46] Thus, there is a genetic predisposition for developing AD. Genome scans have pointed to multiple chromosomes being implicated, with the region of highest linkage found on chromosome 1q21.[1,47] Other reported risk factors include an urban environment, higher socioeconomic status, higher level of family education, female gender (after age 6 years), and a smaller family size.[48]

The *FLG* gene is responsible for the development of the profilaggrin protein, found in the granular layer of the epidermis, and brings structural proteins together to create a strong barrier matrix.[49,50] *FLG* mutations are common particularly among Caucasians. Approximately 10% of individuals of European descent are heterozygous carriers of a loss-of-function mutation in *FLG*, resulting in a 50% reduction in the expression of the protein.[51] When *FLG* mutations are present, disease is more severe and persistent, occurs mainly in early-onset AD, and indicates a propensity toward asthma.[1,52] *FLG* gene defects have also been associated with peanut allergy, contact dermatitis, and infections such as the herpes virus.[39,53] Because *FLG* mutations are identified in only about 30% of European patients with atopic disease, other epithelial genetic variants must also be considered.[1,54,55]

Skin Barrier Dysfunction

The epidermis of the skin consists of several layers that act as barriers to prevent water loss and to protect the body from such foreign substances as microbes and allergens. The *FLG* gene, on chromosome 1q21.3, encodes a key protein in epidermal differentiation.[1] This gene was originally identified as the gene involved in ichthyosis vulgaris, which will be discussed again later,[1,56] and several loss-of-function mutations were identified in European and Japanese patients with AD.[1,57-60] Since then, multiple studies have demonstrated that the *FLG* gene plays a pivotal role in skin barrier function and mutations of the *FLG* gene are a major risk factor for AD.[40,45,61,62] Other skin barrier factors may include a deficiency of skin barrier proteins, increased peptidase activity, lack of certain protease inhibitors, and lipid abnormalities.[40] High-molecular-weight allergens in pollens, house dust-mite particles, microbes, and foods can only penetrate the skin barrier when there is epidermal barrier dysfunction.[63] The strong barrier matrix created by the *FLG* gene, with attached proteins and lipids, forms the stratum corneum, or the outermost layer of the epidermis, which normally provides a barrier to microbes and allergens and minimizes transepidermal water loss.[49] *FLG* mutations or deficiencies result in an abnormality in permeability of barrier function.[62]

Immune Dysfunction

Other immune system–related genes found to be associated with AD include those encoded on chromosome 5q31 to 5q33. These genes code for cytokines that regulate immunoglobulin E (IgE) synthesis: interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-12 (IL-12), interleukin-13 (IL-13), and granulocyte-macrophage colony-stimulating factor.[1] Cytokines are mainly produced by type 1 and type 2 T helper lymphocytes (TH_1 and TH_2, respectively). TH_1 cytokines (IL-12 and interferon-γ suppress IgE production, and TH_2 cytokines (IL-5 and IL-13) increase IgE production.[1,64] Patients with AD have a genetically determined dominance of TH_2 cells that may decrease expression of *FLG* and other molecules found in the skin barrier.[1] Genetically modified mice engineered to overexpress TH_2 cytokines developed skin barrier defects and AD spontaneously.[39] Naturally, many of these cytokines are targets for novel therapies for the treatment of AD.

Atopic March (Triad)

The "atopic march" describes the tendency for AD to precede the development of other atopic diseases such as food allergies, asthma, and allergic rhinitis in a temporal sequence.[65] A 2008 study showed that the march does not necessarily always happen in order, as some patients with asthma develop AD.[66] It has also been reported that while common in childhood, the atopic march can occur at any age.[67] Still, multiple longitudinal studies have provided evidence supporting the atopic march between AD and subsequent allergies, and the interrelationships among subsequent allergic manifestations.[68-76] Patients with atopic dermatitis, allergic rhinitis, and allergic asthma are considered to have the atopic triad. Approximately one-third of patients with AD develop asthma, and two-thirds develop allergic rhinitis.[77,78] Although no recent data exist on the proportion of patients with AD who develop food allergies, it is well known that the 2 conditions co-associate.[79] The common

TABLE 1. Revised Hanifin and Rajka Criteria for Atopic Dermatitis Diagnosis[99]

Essential Features (required)

- Pruritus
- Eczema (acute or chronic)
  - » Typical presentation and age-related patterns
    - › Infants and children: face, neck, extensor involvement
    - › Any age group: history of flexural involvement
    - › Not present in groin and axillae regions

Important Features (present in most cases)

- Early age of onset
- Personal or family history of atopic disease or elevated immunoglobulin E
- Xerosis

Associated Features (nonspecific but may aid in diagnosis)

- Dermatographism
- Keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis
- Ocular/periorbital changes
- Periauricular changes (including fissure at ear lobe creases)
- Perioral changes
- Perifollicular accentuation, lichenification, prurigo lesions (often from scratching)

Exclusionary Conditions (required to properly diagnose AD)

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

link among these allergic disorders is atopy, or the predisposition for IgE-mediated responses to stimuli.[80]

Triggers of Atopic Dermatitis

Triggers are the leading cause of an AD exacerbation, and avoidance of triggers is an important mechanism patients can use to control disease activity.[81] Atopic dermatitis may be triggered by viral infections, food allergens, cosmetics, fragrance, weather, and other causes. Extremes of hot and cold weather are poorly tolerated by patients with AD and can lead to sweating and dry skin, respectively, initiating pruritus. In childhood, wool has been found to be a known trigger of AD.[82] Exposure to environmental allergens such as dust mites, pollens, molds, cigarette smoke, and dander from animals may exacerbate symptoms of AD.[81,83] The role of food as antigens in the pathogenesis of AD is controversial. Food allergens contribute to approximately 40% of AD cases in infancy but are not the cause of AD.[84] An allergist should be consulted to assess the level of allergic severity with respect to food allergens via a risk-benefit ratio to determine if food avoidance or introduction is recommended.[85] The most commonly allergenic foods are eggs, milk, peanuts, wheat, soy, tree nuts, shellfish, and fish.[83]

Diagnostic Criteria

Classification

An AD diagnosis is made clinically through an extensive history and physical examination that relies strongly on clinical presentation. Multiple groups have developed classification criteria over the years to aid in diagnosis.[5,86,87] The Hanifin and Rajka criteria are the most recognized set of diagnostic criteria and are widely considered to be the gold standard for AD diagnosis.[5,87] The diagnostic criteria are very thorough, requiring 3 of 4 major criteria and 3 of 23 minor criteria be met for diagnosis. The original version created in 1980 is very comprehensive and applicable to clinical trials, but the large quantity of criteria made its application elsewhere impractical. The United Kingdom (UK) Working Party specifically took on the task of scaling down the criteria to a core set that was amiable to use in clinical practice, consisting of 1 mandatory and 5 major criteria and no requirement for laboratory testing.[88,89] However, skin biopsy or other tests may be necessary to exclude other medical conditions. Both the Hanifin and Rajka and the UK Working Party AD diagnostic criteria have been tested and validated in multiple studies and populations.[5,89-98] An important limitation of the UK Working Party AD criteria is the inability to apply them to very young children, but, notably, revisions have been proposed to address this concern. Therefore, the Hanifin and Rajka criteria were further revised by an American Academy of Dermatology consensus conference.[99] The goal of the revisions was to make the criteria more streamlined and applicable to the broad range of ages of individuals affected with AD (**Table 1**[99]).[99] These 2003 criteria have not been validated, but the work group deemed them appropriate for use in clinical practice for diagnosing infants, children, and adults.

Exclusion of Diseases in Diagnosis of AD

The diagnosis of AD should include exclusion of other similar skin conditions (Table 1[99]).[99] There are multiple skin conditions that can be confused with, coexist with, and/or complicate AD.[100] Seborrheic

dermatitis (SD) is a common inflammatory skin condition that is difficult to distinguish from AD, especially in infancy where they can occur concomitantly or separately.[100] SD is distinguished by a lack of excoriations and sleep impairment and, unlike AD, usually resolves before the age of 2 years.[100] Additionally, SD lesions are typically thick, greasy, white, off-white, or yellow in appearance. In patients with darker skin types, lesions often have hypopigmentation.[100] Psoriasis is another inflammatory skin condition that should be ruled out in patients suspected of having AD. Since scaling in psoriasis is typically more prominent and distribution of lesions includes the face, it is possible for misdiagnosis with AD.[100] Psoriasis is frequently found in the diaper area (unlike AD) and includes nail involvement, which can help distinguish between the 2 skin conditions. Contact dermatitis is the most common form of dermatitis and is characterized by erythema and edema. It can occur simultaneously with other inflammatory skin conditions and complicate AD.[100] Infestations such as scabies should also be excluded when diagnosing AD. Scabies is an allergic response to the mite, eggs, and feces of *Sarcoptes scabiei*. The reaction is characterized by small, red papulovesicles or eczematous lesions.[100] Gradual onset, lack of dry skin, and other family members experiencing itch during the same time frame help to confirm diagnosis. It can also be differentiated from AD by visual inspection of the mite's linear burrows.[100] Other skin conditions that are commonly associated and/or confused with AD are pityriasis alba, keratosis pilaris, ichthyosis vulgaris, and dermatographism, which will be discussed in detail later in this article.[52]

Biomarkers

There are no current reliable biomarkers that can be used to routinely diagnose and differentiate AD from other similar skin conditions. The most common associated laboratory value in current practice is IgE, with approximately 80% of patients with AD experiencing an elevated level.[5] However, it is important to note that there are several limitations with this potential biomarker. Namely, 20% of the AD population does not present with elevated IgE; some individuals develop elevated IgE later; and elevated allergen-specific IgE levels are nonspecific, having been found in approximately 55% of the US general population.[5,101,102] Furthermore, IgE is not a reliable indicator, as some patients with severe disease present with normal IgE levels, and IgE can be elevated in multiple nonatopic conditions (eg, parasitic infection, certain cancers, and autoimmune diseases).[5,101,103,104]

Discovery of new T-lymphocyte subsets and novel cytokines and chemokines have created numerous opportunities for the development of new biomarkers.[5] Potential options include serum levels of CD30, macrophage-derived chemoattractant (MDC), interleukins (IL-12, IL-16, IL-18, IL-31), and thymus and activation-regulated chemokine (TARC). Some of these new biomarkers have correlated with AD severity, but none have shown reliable sensitivity or specificity for AD to support regular clinical use for diagnosis and monitoring.[5]

TABLE 2. Skin Features Associated With Atopic Dermatitis in Children and Adults[83]

Skin Feature	Skin Feature Description
Atopic pleat (Dennie-Morgan fold)	Extra fold of skin that develops under the eye
Cheilitis	Inflammation of the skin on and around the lips
Hyperlinear palms	Increased number of skin creases on the palms
Hyperpigmented eyelids	Eyelids that have become darker in color from inflammation or hay fever
Ichthyosis	Dry, rectangular scales on the skin
Keratosis pilaris	Small, rough bumps, generally on the face, upper arms, and thighs
Lichenification	Thick, leathery skin resulting from constant scratching and rubbing
Papules	Small raised bumps that may open when scratched and become crusty and infected
Urticaria	Hives (red, raised bumps) that may occur after exposure to an allergen, at the beginning of flares, or after exercise or a hot bath

Source: National Institute of Arthritis and Musculoskeletal Skin Diseases.

Clinical Presentation

Atopic dermatitis is considered to be a chronic relapsing inflammatory skin condition. As a result, it generally presents in 3 different clinical phases: 1) acute AD (a vesicular, weeping, crusting eruption); 2) subacute AD (dry, scaly, erythematous papules and plaques); and 3) chronic AD (lichenification, thickening, from repeated scratching).[2] AD is commonly localized to the flexural surfaces of the body, anterior and lateral neck, eyelids, forehead, face, wrists, dorsa of the feet, and hands.[2] As a result of the broad range of severity and presentation, differential diagnosis is essential to the proper diagnosis of AD (see **Table 2**[83]).[52,99] In addition to the clinical phases, the disease course of AD is not static but rather defined by a pattern. A study conducted in 2004 looked at disease course, with AD falling into 1 of 3 disease patterns: 1) persistent (19%; AD at every follow-up until age 7 years); 2) intermittent (38%; early AD not fitting persistent or remission criteria); or 3) remission (43%; no AD after the age of 2 years).[9] Thus, it is important for healthcare providers to be able to recognize and classify AD so that appropriate treatment can proceed.

Age and Disease Presentation

The clinical disease presentation (Table 2[83])[52,99] varies based on the age of the individual affected. In infancy, AD is generally recognized soon after birth, as xerosis occurs early and can involve the entire body, usually excluding the diaper area. The first presentation

in infancy is an erythematous papular skin rash that can affect the creases, particularly on the front of the elbow and behind the knee (antecubital and popliteal fossa).[83,105] This patchy skin rash can progress to redness, scaling, and exudation with a centrifugal distribution affecting the cheeks, forehead, scalp, chin, and behind the ears while sparing the nose.[83,105] Over time, the lesions can spread to the lower legs with potential involvement anywhere on the body but usually still sparing the diaper area and the nose.[83] Uncontrollable itching is characteristic of developed lesions leading to rubbing of the face by the infant to help control the itch. Scratching can develop very early in infants and those impacted by AD can scratch continuously.[83] Excessive rubbing or scratching can result in crusted erosions, excoriation, and subsequent development of secondary infections.[83]

In childhood, xerosis is often generalized, causing rough, flaky, or cracked skin. Lichenification, thickening of the skin, is characteristic in older children and adults.[105,106] Lichenification is representative of repeated rubbing of the skin and seen mostly over the folds, bony protuberances, and forehead.[105] Pallor of the face is common; erythema and scaling occur around the eyes with Dennie-Morgan folds often seen as well.[105] Dennie-Morgan folds are commonly seen under the eyes of children with allergies. Flexural creases, especially the antecubital and popliteal fossae, and buttock-thigh creases are often affected.[105] Excoriations and crusting are also common and can lead to secondary infections; however, it is important to distinguish, as both AD and infections can produce oozing and crusting.[105]

In adulthood, xerosis is prominent and lesions are more diffuse with underlying erythema. The face is commonly involved, presenting as dry and scaly.[105] Like AD in childhood, lichenification may also be present. In addition, a brown macular ring around the neck, representing a localized deposit of amyloid, may also be present.[105]

Hallmark Essential Feature of AD

Pruritus, or itching, is the first essential feature required for diagnosis of AD and the leading symptom that characterizes AD.[5,52] Unfortunately, with this type of atopic skin condition, scratching and rubbing only further irritate the skin and worsen the itchiness experienced by the patient. Itching can also occur during the night and can further exacerbate AD, as there is no conscious control of scratching while sleeping.[83,107] Itching can be triggered by multiple factors, such as heat and perspiration (96%), wool (91%), emotional stress (81%), certain foods (44%), upper respiratory infections (36%), and house dust mites (>35%).[108] Furthermore, once initiation of itching occurs, the surrounding skin (regardless of inflammation) can be very sensitive and involuntarily react (alloknesis) to other stimuli such as light and can begin to itch.[108] Thus, patients with AD with alloknesis can begin itching simply from their skin being touched by mechanical factors such as clothing.[108]

Other Skin Features Commonly Associated With AD

There are 4 features that are commonly associated and/or confused with AD that are important to distinguish from AD: 1) Pityriasis alba is characterized by red, scaly patches that eventually resolve, leaving areas of hypopigmentation. They occur most commonly on the face, upper extremities, and trunk, and may be more pronounced with sun exposure, as surrounding skin tans.[52] 2) Keratosis pilaris is a harmless skin condition that results in tiny bumps on the skin due to plugs of dead skin cells. Patients complain of skin that is rough and "plucked chicken skin" in appearance on the upper arms, thighs, cheeks, and buttocks. 3) Ichthyosis vulgaris results in a "fish-scale" appearance most commonly seen on the lower legs, but it can affect other locations. Approximately half of patients with ichthyosis vulgaris develop AD and it is associated with earlier onset of disease and increased severity of AD.[100] 4) Dermatographism (aka "skin writing") occurs as a result of scratching the skin, producing a reddened raised wheal that appears within 5 minutes of stimulation and can last for up to 30 minutes.

AD-Associated Complications

Bacterial Infections: AD is associated with decreased production of antimicrobial peptides in the skin and an unusual cutaneous microbiome, with decreased diversity and increased *Staphylococcus aureus* colonization.[109,110] Approximately 80% to 90% of patients with AD are carriers for *S. aureus*.[111] Patients with AD who are colonized by *S. aureus* are not necessarily infected; however, they are at risk for superinfection of their cutaneous lesions (impetiginization).[110] Patients with AD are, however, at increased risk for colonization with methicillin-resistant *S. aureus* (MRSA), compared with the general population.[112] Those colonized with MRSA are also at an increased risk for skin infection compared with those colonized with methicillin-sensitive *S. aureus*.[113,114]

Viral Infections: Patients with AD are at a higher risk for eczema herpeticum (EH), an acute, potentially life-threatening viral infection caused by the herpes simplex virus.[100] Approximately 20% of patients with AD develop EH.[115] EH is more common among patients with AD with severe disease or IgE-mediated disease. Molluscum contagiosum (MC) is a benign viral skin infection that presents as flesh-colored, pink, or pearly white papules. The virus can last an average of 1 to 2 years and can leave pitted scarring.[52] The MC virus in patients with AD can be more involved, leading to molluscum eczema, in which dermatitis develops surrounding the molluscum lesions.[100]

Fungal Infections: These may also invade compromised skin, leading to colonization with tinea or yeast. Appropriate cultures may be needed in those patients who have risk factors for tinea or yeast colonization or who remain unresponsive to treatment. Evidence is lacking for increased risk due to AD; however, the broken skin, erosions, and excoriations that are common in patients with AD can become colonized.[100]

AD-Associated Comorbidities

Recent studies have linked AD with nonatopic comorbidities such as attention-deficit/hyperactivity disorder and speech disorders.[116,117] Anxiety and depression have also been associated but are more common among adults with AD.[118,119] It is unclear why these associations exist in patients with AD; however, psychosocial impacts, such as embarrassment and sleep disruption, may contribute.[110] Other comorbidities in children with AD include headaches,[31] anemia,[120] and epilepsy.[121] Both adults and children have been associated with injuries such as fractures, and with low bone mineral density (BMD), possibly related to the use of oral corticosteroids for AD.[122-124] The lower BMD and fracture risk may also be associated with the cutaneous inflammation in AD that leads directly to bone loss.[125] Recent attention has focused on whether there is an association between AD and increased cardiovascular (CV) risk. AD has been consistently associated with obesity in both children and adults, and with other CV risk factors such as hypertension, hypercholesterolemia, and diabetes.[126-128] There is controversy with respect to risk of CV outcomes such as myocardial infarction and stroke in patients with AD. Some studies report an increased CV morbidity[129,130] and other studies showed no independent association[131,132] in patients with AD. A 2016 study from the Nurses' Health Study 2 found no significant association between AD and myocardial infarction or stroke.[132] This study controlled for other AD comorbidities, including asthma, suggesting that comorbid asthma may be driving the CV risk.

Conclusion

In summary, AD is the most common skin disease affecting children. The burden of disease from AD is significant for not only the patients but also their families. The disease can persist throughout a patient's lifetime, notably affecting quality of life, and the costs associated with AD are difficult for patients and their family members to manage. In the last 3 decades, there has been substantial progress with respect to understanding the pathogenesis of AD. These new insights related to the genetic, immunologic, and environmental impacts have paved the way for future novel treatments. Early diagnosis and treatment may help decrease the morbidity of the disease and prevent progression to other associated atopic diseases.

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Treatment and Managed Care Issues of Atopic Dermatitis

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ABSTRACT

The specific cause of atopic dermatitis (AD) is not known. It is a multifactorial disease involving environmental agents, immune dysregulation, genetic predisposition, and defects in skin barrier function. Patients are typically classified as having mild, moderate, or severe disease. Most patients with AD can control their symptoms with various combinations of moisturizers, conventional prescription therapies, and lifestyle modifications, while patients with more severe disease may require adjunctive treatment with phototherapy, biologic treatments, or systemic immunosuppressants. As a result, patient-centered treatment plans are critical to patient care. The appropriate use of nonpharmacologic and pharmacologic treatment interventions combined with patient-specific written action plans could improve both patient health and medication outcomes.

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For author information and disclosures, see end of text.

The etiology of AD is not well understood. Evidence suggests that AD is a multifactorial disease involving environmental agents, immune dysregulation, genetic predisposition, and defects in skin barrier function.[1] Diagnosis of AD is complicated by variability in clinical presentation and the lack of consensus surrounding diagnostic criteria.[2] Patients are typically classified as having mild, moderate, or severe disease. The majority of patients can control AD symptoms with various combinations of moisturizers, conventional prescription therapies, and lifestyle modifications. Patients with more severe disease may require adjunctive treatment with phototherapy, biologic treatments, or systemic immunosuppressants. Consequently, accurate diagnosis and individualized patient-centered treatment plans are critical to patient care.

Nonpharmacologic Interventions

Topical Moisturizers and Prescription Emollient Devices

Maintaining skin hydration and preventing transepidermal water loss (TEWL) are essential components of AD treatment. Over-the-counter (OTC) topical moisturizers are applied to the skin to prevent dryness and TEWL. Studies show that the application of topical moisturizing agents alone reduces symptom severity[3,4] as effectively as topical corticosteroids (TCSs) used in patients with AD.[5] In a 3-week study involving children with mild-to-moderate AD, the application of desonide 0.05% every other day plus 2% sunflower oil twice daily was as effective as once- or twice-daily desonide alone ($P = .83$).[6] The properties and composition of topical moisturizers can vary greatly, making a given product more or less suitable for an individual. Traditional agents contain varying amounts of the following: 1) emollients that soften skin by filling in spaces between desquamating corneocytes; 2) occlusive agents that create a hydrophobic film on the surface of skin to prevent TEWL; and 3) humectants that attract and retain water from the deeper dermis.[7] Topical moisturizers are available as oils, lotions, creams, ointments, and gels. Lotions often contain preservatives and fragrances, which can function as irritants to the skin; they

also have a high water content, which creates an additional drying effect. Ointments have the advantage of generally being preservative free; however, cosmetic acceptability of ointments is a concern due to their greasy texture and may inhibit adherence.[8] As a result, the following factors must be taken into consideration when helping patients and caregivers select a topical moisturizer: ease of application, how it smells, how well it is absorbed, and how it feels on the skin.[9] Regardless of the particular product and delivery system that is used, the selected moisturizer must be one that the patient feels comfortable using on a daily basis, given our current understanding of barrier dysfunction in the pathogenesis of AD. Topical moisturizers enhance the hydration of the skin and minimize flare-ups and complications of AD. Therefore, they are considered an integral component of the maintenance plan. Application should be individualized for patients and can range from daily to multiple applications in a day. Topical moisturizers are best when applied soon after bathing to optimize skin hydration.[8,10]

In addition to topical moisturizers, prescription emollient devices (PEDs) are used to prevent TEWL and to improve skin hydration in patients with AD. PEDs are different from OTC moisturizers in that they are FDA-approved, 510(k) devices that provide a structural role in skin barrier function; they do not exert their effects by any chemical actions.[8] They are generally applied to the skin 2 to 3 times daily depending on the specific agent. Comparative studies evaluating the cost-effectiveness of PEDs and OTC moisturizers have produced mixed results.[11,12] In an investigation of treatment cost, a total of 39 patients aged 2 through 17 years with mild-to-moderate AD were randomized to receive 1 of the following treatments: glycyrrhetinic acid containing PED, ceramide-dominant PED, or OTC petrolatum-based topical moisturizer. Patients were instructed to apply the study treatment 3 times daily for 21 days. No significant between-group differences were observed at days 7 or 21, but OTC petrolatum-based moisturizer was nearly 50 times more cost-effective than either PED.[12]

Notably, head-to-head trials comparing specific topical moisturizing agents are limited. As a result, the selection of moisturizing agents is highly dependent on patient preference and cost. There is no published guidance on the correct order of application of moisturizers and prescription AD treatments. One study showed that the order of TCSs and moisturizers did not matter as far as influencing severity of disease.[13] Product labeling of topical calcineurin inhibitors (TCIs) indicates that moisturizers may be applied after use.[14,15]

Bathing and Wet Wrap Therapy

While the daily application of topical moisturizers is an integral part of managing AD, bathing and wet wrap therapy are additional interventions that can reduce disease severity. There are no data to suggest an appropriate frequency or duration of bathing. Expert consensus indicates that bathing up to 1 time daily for 5 to 10 minutes with warm water can remove excess scale.[8] Hypoallergenic and fragrance-free cleansers that support optimal skin surface pH are recommended for use on a limited basis. After bathing, topical moisturizers should be applied after gently toweling skin to improve skin hydration.[8] For areas of the body with significant lesions, the nighttime soak-and-smear technique has proved to be a simple, inexpensive method that provides symptomatic improvement.[16] This technique involves a 20-minute soak with plain water followed immediately (no drying skin) by smearing a mid- to high-potency TCS ointment on damp skin; this functions to trap water, allowing deeper penetration of the corticosteroid. Time to symptomatic improvement correlates with underlying disease severity, although most patients show improvement within several days to 2 weeks of continued application. If the patient has moderate-to-severe disease and a history of *Staphylococcus aureus* infection, bleach baths 2 to 3 times weekly may help decrease the number of local skin infections and reduce the need for antibiotics in patients with AD. Bleach baths are prepared by adding a quarter cup to a half cup of common bleach solution to approximately 1 full tub of bath water.[17] Huang et al conducted a randomized, investigator-blinded, placebo-controlled study (N = 31) that showed a greater mean reduction in Eczema Area and Severity Index (EASI-75) scores in patients who received diluted bleach bath treatment compared with placebo group at both 1-month and 3-month follow-ups.[18]

Wet wrap therapy has proved to be an effective treatment in patients with moderate-to-severe disease, especially during periods of significant flares.[19] Application techniques that have been reported in literature vary. Briefly, most wet wrap dressings involve the application of a TCS that is covered by wet gauze or bandages; a dry cotton second layer is then applied to maintain skin hydration. Wet wraps are typically worn for several hours to 1 full day and repeated for several days to 2 weeks. The impact of wet wrap therapy was evaluated in 72 children with moderate-to-severe disease treated with wet wrap therapy and monitored for outcomes within a supervised multidisciplinary AD treatment program. Wet wraps were left in place a minimum of 2 hours and were generally removed after 4 to 6 hours. Improvement in disease severity was assessed using the Scoring Atopic Dermatitis (SCORAD) instrument. Disease severity at admission and at discharge showed significant differences in mean $\pm$ SD values, of 49.68 $\pm$ 17.72 versus 14.83 $\pm$ 7.45, respectively (t, 18.93; df, 71; P <.001). The average duration of treatment was 7.5 days, ranging from 2 days up to a maximum of 16 days.[20] Due to the occlusive barrier that is created with wet wrap therapy, secondary infections, maceration of the skin, and systemic bioactivity of TCSs can occur when wet wraps are overused or used incorrectly.[8,17] Consequently, patients must be supervised closely, ideally by a medical provider who has expertise in the use of wet wrap interventions.

TABLE. Number of FTUs Required for Select Body Sites on Children[29]

Age	Number of Fingertip Units				
	Face and Neck	Arm and Hand	Leg and Foot	Trunk (front)	Trunk (back)
3 to 6 months	1	1	1.5	1	1.5
1 to 2 years	1.5	1.5	2	2	3
3 to 5 years	1.5	2	3	3	3.5
6 to 10 years	2	2.5	4.5	3.5	5

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Pharmacologic Interventions

Topical Corticosteroids

When AD is not controlled by nonpharmacologic interventions, TCSs are recommended as first-line prescription treatments. Multiple studies support the use of TCSs, and they are the standard to which other AD therapies are compared.[8] TCSs act on a wide range of immune cells, suppressing the release of proinflammatory cytokines while exerting antiproliferative effects on several cell types, including T-lymphocytes. The potency of TCSs is based on their vasoconstricting ability and ranked on a scale of 1 through 7.[8] Very-high-potency agents are ranked in class I, whereas the least potent corticosteroids are ranked in class VII.[8,21] Low- to mid-potency agents are preferred for children as well as for body sites with thin skin due to an increased likelihood of systemic absorption. The face, neck, and skin folds are common areas of the body where low-potency TCSs are preferred.[22] Available vehicles include foams, ointments, solutions, creams, gels, and lotions.

Despite the extensive use of TCSs, there are limited data regarding optimal duration and frequency of therapy.[23] The majority of studies evaluating the safety and efficacy of TCSs involve once- or twice-daily dosing.[24] Some experts recommend using a short burst of a high-potency TCS to rapidly control active disease, followed by a quick taper with a low-potency TCS. Others use the least potent TCS that is thought to be effective and titrate upward as needed.[8] During periods of acute flares, the continuous use of TCSs is recommended until inflammatory lesions have significantly improved[25]; however, prescribers may recommend continued use of TCSs for up to 3 days beyond clearance.[26] The median time to clinical resolution is dependent on disease severity and may require daily use of TCSs for up to multiple weeks at a time. In the past, once clinical resolution of flares was achieved, TCS therapy was stopped, changing to daily use of topical moisturizers and reinstituting TCSs during subsequent relapses.[8] However, studies demonstrate that a proactive dosing strategy of 2 to 3 applications per week on areas that commonly flare may be a more cost-effective treatment approach.[27] This practice is supported by treatment guidelines from the American Academy of Dermatology with both the TCSs or TCIs for the prevention of AD flares. Continuous application of TCSs for extended periods of time should be avoided.[25]

Results from clinical studies suggest that TCSs are associated with few adverse effects (AEs) when applied appropriately. Skin atrophy, or thinning of the skin, is typically the greatest concern among patients and caregivers because it can lead to over-caution and suboptimal treatment. Many TCS-related AEs resolve after discontinuing use; in some cases, it may take months.[28] Therefore, it is important that patients and caregivers understand the appropriate quantity of drug that is required for each body site. The fingertip unit (FTU) is a reference tool that qualitatively describes the amount of drug to be used.[29] It is the amount of drug removed from a tube with a 5-mm diameter nozzle, applied from the tip of the index finger to the distal skin crease.[29] One FTU is approximately equal to 0.5 grams, which effectively covers an area equivalent to 2 adult hands with fingers together. The table illustrates the number of FTUs required for specific body sites on children (**Table**[29]).[29]

Topical Calcineurin Inhibitors

Tacrolimus ointment and pimecrolimus cream are TCIs that are indicated as second-line treatments in patients with AD.[8] Calcineurin, found in the skin, regulates the activity of transcription factors that control cell division and early stages of T-cell activation. Through inhibition of calcineurin, tacrolimus and pimecrolimus exhibit their clinical effect. Tacrolimus ointment is approved for moderate-to-severe disease; the 0.1% ointment is approved for patients ≥16 years of age and the 0.03% ointment is approved for patients ≥2 years of age.[15] Pimecrolimus is approved for mild-to-moderate AD and is available as a 1% cream for patients ≥2 years of age.[14] The key benefit of TCIs is that they can be used in place of TCS with fewer associated AEs. Pharmacokinetic studies demonstrate that systemic absorption is negligible when TCIs are applied according to product labeling.[30,31] As a result, they are commonly used on body sites with thin skin and when continuous treatment or widespread application is required.[8] Expert consensus recommends that TCIs should be considered in the following clinical conditions: 1) patients who are refractory to TCS; 2) treatment of the face, neck, and skin-fold; 3) patients who experience steroid-induced atrophy; and 4) long-term continuous therapy with TCSs.[8] TCIs are recommended to be used twice daily and should not be used with occlusive dressings; patient re-evaluation is recommended if symptoms persist beyond 6 weeks. Similar to therapeutic trends for TCSs, multiple studies have demonstrated that proactive 2- to 3-times-weekly dosing of TCIs provides incremental health benefits at a lower cost compared with traditional TCI dosing regimens.[32,33] The most common AEs with TCIs are stinging and burning, which are usually transient and resolve after several days of treatment.[34]

In January 2006, the FDA issued a black box warning for TCIs based on a theoretical risk of malignancy, which remains in effect

to this date.[35] This concern stemmed from cases of skin cancer and lymphoma that were observed with the use of high-dose oral calcineurin inhibitors in transplant recipients as well as dose-ranging studies performed in animals. In 2011, the FDA Pediatric Advisory Committee reviewed multiple postmarketing studies and concluded that the risk of malignancy following TCI use is no higher than what is observed in the general population.[36] The precautionary warning is still listed in product labeling.

Topical Crisaborole

The lack of suitable alternatives leads to the continued use of TCSs as first-line AD treatments. However, the development of newer agents with improved safety profiles may influence changes in clinical practice. In December 2016, the FDA approved topical crisaborole, which is the first new AD treatment in more than a decade. Crisaborole ointment, 0.2%, is a nonsteroidal phosphodiesterase-4 (PDE-4) enzyme inhibitor that is indicated for mild-to-moderate AD.[37] PDE-4 inhibits cyclic adenosine monophosphate (cAMP), which is believed to play a significant role in the release of intracellular proinflammatory cytokines. Crisaborole inhibits PDE-4 and its ability to degrade cAMP, thereby suppressing the downstream production and release of proinflammatory mediators in atopic skin. Initial pharmacokinetic studies show topical crisaborole is rapidly absorbed and metabolized to inactive metabolites that have no significant effects on PDE-4 activity.[38] Consequently, the risks of both systemic exposure and AEs are low.[38,39] Crisaborole is applied twice daily and is approved for use in patients ≥2 years of age.

Multiple studies support the safe and effective use of topical crisaborole in mild-to-moderate AD. Two randomized, double-blind, vehicle-controlled, phase 3 studies (AD-301 and AD-302) were conducted to evaluate the safety and efficacy of crisaborole over a period of 28 days. Key inclusion criteria required patients to be aged 2 years or older and have a baseline Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) AD.[40] The primary endpoint was an ISGA score at day 29 of clear (0) or almost clear (1), with a 2-grade or greater improvement from baseline. Additional endpoints assessed the severity of pruritus and signs of AD. Patients were instructed to apply the study drug twice daily throughout the study period to all areas affected by AD; the scalp area was not included because of potential patient dissatisfaction with cosmetic effects involving the head. Patients were permitted to continue the use of topical moisturizers to manage dry skin around the areas of crisaborole- or vehicle-treated lesions. At day 29, more patients in the crisaborole treatment group achieved an ISGA score of clear (0) or almost clear (1) compared with vehicle (AD-301: 51.7% vs 40.6%, $P = .005$; AD-302: 48.5% vs 29.7%, $P < .001$). In addition, more crisaborole-treated patients demonstrated improvement in pruritus at day 29; the difference was statistically significant ($P = .002$). Additionally, more crisaborole-treated patients had reductions in mean disease severity, with statistically significant results (pooled data, erythema: $P < .001$; exudation: $P = .001$; excoriation: $P < .001$; induration: $P = .002$; lichenification: $P < .001$). Crisaborole-treated patients demonstrated a low incidence of treatment-related AEs. Application site pain was the most commonly reported event, which occurred in 4.4% of crisaborole-treated patients versus 1.2% receiving placebo.[40]

Dupilumab

A second new agent, dupilumab, was FDA approved in March 2017 for the treatment of patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies, or for patients in whom the use of such therapies is medically inadvisable. Dupilumab is a fully human monoclonal antibody that inhibits interleukin-4 and interleukin-13 intracellular signaling, which is believed to play an important role in the inflammatory process of myriad allergic diseases, including asthma and AD.[1,41]

Data from SOLO 1, SOLO 2, and CHRONOS clinical trials were instrumental in the regulatory approval of dupilumab. SOLO 1 and SOLO 2 were 2 identical 16-week, randomized, placebo-controlled, phase 3 trials that evaluated the safety and efficacy of subcutaneous (SC) dupilumab compared with placebo in 671 and 708 patients, respectively.[42] Key inclusion criteria required patients to be aged 18 years or older, have a diagnosis of moderate-to-severe AD for which topical treatment did not provide adequate control or was medically inadvisable, and an ISGA score of 3 (moderate) or 4 (severe). Patients received a 600-mg SC dose of dupilumab at day 1, followed by SC injections of dupilumab 300 mg weekly, every other week, or placebo; each study group was also required to apply topical moisturizers twice daily throughout the 16-week trial period. In SOLO 1, 38% of patients receiving dupilumab every other week and 37% of patients receiving dupilumab once weekly achieved the primary endpoint of an ISGA score of clear (0) or almost clear (1), compared with 10% receiving placebo ($P < .001$ for both comparisons). In SOLO 2, 36% of patients receiving dupilumab every other week and 36% of patients receiving dupilumab once weekly achieved an ISGA score of clear (0) or almost clear (1) compared with 8% receiving placebo ($P < .001$ for both comparisons). In both trials, dupilumab-treated patients demonstrated at least a 3- to 4-point improvement in pruritus, and EASI-75 scores improved by at least 75% from baseline to week 16 compared with placebo ($P < .001$ for both comparisons). Clinically significant improvements were also observed regarding anxiety and depression, health-related quality of life, and patient-reported symptoms of AD.[42]

In the CHRONOS study, 740 patients with moderate-to-severe disease who were inadequately controlled with topical medications and had a baseline ISGA score of moderate (3) or severe (4) were randomly assigned to 1 of 3 treatment groups (all in combination with the daily application of a low- to mid-potency TCS): dupilumab

300 mg SC once weekly, dupilumab 300 mg SC every other week, or placebo.[43] In the dupilumab-treatment groups, a 600-mg dose was administered at day 1 followed by the aforementioned treatment regimens. The primary endpoints of the study were the percentage of patients who achieved an ISGA score of clear (0) or almost clear (1) as well as a reduction from baseline of at least 2 points at week 16. Thirty-nine percent of patients who received either dupilumab 300 mg weekly plus a TCS or dupilumab 300 mg every other week plus a TCS achieved an ISGA score of clear (0) or almost clear (1) at 16 weeks, compared with 12% receiving a TCS and placebo (P <.0001). In addition, 64% of patients who received dupilumab 300 mg weekly plus a TCS, and 69% of patients who received dupilumab 300 mg every other week plus a TCS, had EASI-75 scores improve by at least 75% from baseline to week 16, compared with 23% receiving a TCS and placebo (P <.0001). The secondary endpoint 52-week results regarding the percentage of patients who achieved either an ISGA score of clear (0) or almost clear (1) or EASI-75 were nearly identical to week 16 results. The most common AEs that occurred in early- and late-phase studies of dupilumab were injection-site reactions, headache, mouth sores, and conjunctivitis; all were reported with a higher frequency compared with placebo.[42,44]

Dupilumab is FDA approved for use in adult patients only. The recommended dosing regimen includes an initial dose of 600 mg (two 300-mg SC injections administered at different locations), followed by 300 mg given every other week. It is available in 2 product formulations: a 300 mg per 2 mL prefilled syringe with or without a needle shield. Dupilumab should be stored in the refrigerator; once removed from the refrigerator, syringes should be used within 14 days or discarded. Due to an increased risk of ocular complications with dupilumab, patients should be advised to consult their healthcare provider if new-onset or worsening eye symptoms develop, such as redness, itching, or tearing of the eye.[45]

Phototherapy and Systemic Agents

Some patients with AD are refractory to optimized topical regimens and require phototherapy or systemic immunosuppressants. Different forms of phototherapy have distinct profiles that must be considered before treatment. As a result, all forms of phototherapy are typically performed under the guidance of physicians who specialize in phototherapy techniques. Narrowband ultraviolet B phototherapy has emerged as the modality of choice by providers when considering its availability, low-risk profile, and relative efficacy.[10] There are few studies that compare the efficacy of systemic immunosuppressants for the management of AD, and none are FDA approved for use. The most commonly prescribed therapies include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.[46] Available data suggest that each agent is effective for the treatment of AD[47-50]; however, optimal dosing strategies and duration of treatment are unclear. In addition, product labeling and clinical guideline recommendations should be consulted as monitoring parameters for each individual agent are significant.

Managing Atopic Dermatitis in the Managed Care Environment

Burden of Disease

The public health burden of AD is considerable. Patients with AD incur more costs, lose more work days, and have poorer overall health than those without AD. A recent analysis of adult patients with AD showed that patients paid $37.7 billion in out-of-pocket healthcare costs in 2010; adult patients with AD paid $371 higher out-of-pocket costs per person-year compared with those without AD.[51] In addition, a total of 73 million weighted days of lost work occurred in 2010. Adults with AD are 53% more likely than those without disease to have 6 or more lost workdays from any cause. AD has a significant impact on the mental health of patients as well. In the International Study of Life with Atopic Eczema, more than one-half of patients reported symptoms of depression and exacerbations affecting sleep patterns an average of 14.6 nights per flare, corresponding to 162 nights per year.[52] Every missed opportunity for improving healthcare may result in unnecessary patient suffering. Patient-centered care in collaboration with various medical providers is an important way to optimize health and medication outcomes.

Pharmacist-Patient Care Process

All patients and families should be educated on skin care, considering that the efficacy of AD treatment regimens is only as good as each patient's ability and willingness to implement clinical recommendations. Coordinated, interprofessional, patient-centered care is a method that has been shown to improve patient outcomes and is a key component in the evolving healthcare model. In recent years, the Joint Commission of Pharmacy Practitioners developed the pharmacist-patient care process, which provides a framework for delivering consistent pharmacy care in any practice setting.[53] The 5 basic components of the pharmacist-patient care process are: collect, assess, plan, implement, and follow up.

An essential first step in the pharmacist-patient care process is developing a relationship with the patient and family that supports effective communication. To understand the clinical status of each patient, the pharmacist must collect patient- and family-specific information to assess financial resources available to obtain medications, previous treatment failures, current medications, disease severity, and patient-specific AD triggers.[2] Once subjective and objective data are collected, prioritizing patient-specific, drug-related problems and aligning treatment goals are vital. A primary goal in the treatment of AD is to improve medication adherence and reduce unnecessary costs. Frequently, treatment failure or suboptimal responses to therapy can be attributed to medication nonadherence. Common reasons for patient and/or caregiver nonadherence include patient

or caregivers being unaware of the correct frequency and the type of medication that should be applied; lack of motivation and not refilling prescriptions; perception that treatment does not work, medication is cosmetically unacceptable, or medication is too painful to apply; or medication has unacceptable AEs.[54] In a study evaluating medication adherence, 37 patients treated with 0.1% triamcinolone ointment and instructed to apply medication twice daily to affected skin area for a total of 8 weeks.[55] The average adherence from baseline to study completion was only 32%. One of the most difficult problems regarding medication adherence is steroid phobia, which is fear and anxiety on the part of patients that TCSs cause harm. As many as 80% of patients admit to concerns about TCSs and nearly 40% use them less frequently or for shorter periods than prescribed.[52,56] Educating patients and families to be aware of the signs of skin atrophy, as well as explaining that mild cutaneous AEs are reversible with time, may lessen anxiety about TCSs and improve adherence. In addition, parental education regarding the appropriate application of topical treatments should not be overlooked. One survey reported that fewer than 5% of parents were provided instruction or demonstration about the application of topical therapies by medical providers.[57] Considering children are disproportionately affected by AD, parental involvement and education are vital to help reduce flares and extend periods of remission in children with AD.

Patient and family concerns about AD and related treatments may be overcome with written action plans. AD action plans include written instructions about how and when to apply topical and systemic medications, when to increase or decrease treatment, appropriate bathing practices, and when to seek medical treatment. A sample AD action plan from the American Academy of Dermatology website is illustrated in the **Figure**[58].[58] The efficacy of written action plans has been evaluated in several small studies. In a demonstration of AD action plan efficacy, AD action plans were associated with significant improvements in patients with AD, including patients understanding of benefits and risks associated with prescribed medications ($P = .02$), recognition of AD exacerbating factors ($P = .02$), and adjusting treatment based on disease severity ($P < .01$), compared with verbal instruction.[59] In a separate study, as many as 80% of parents reported lower disease severity in their children after the implementation of written action plans, and of those children whose AD improved in severity, 68% of parents attributed the written action plan as a contributing factor.[60]

The pharmacist-patient care process begins with the initial encounter and continues through each follow-up visit. All AD treatment plans should include scheduled follow-up visits to assess medication adherence, disease severity, overall patient satisfaction, and the need for physician referral. Several instruments are available to assess disease severity but there is no consensus of a "gold standard" among providers.[8,61] Each instrument assigns a patient a severity score that is based on multiple factors, such as body surface area affected, course of disease, and severity of pruritus. Every pharmacist is encouraged to incorporate some method of consistent grading of AD symptoms into daily practice to effectively monitor clinical progression. Two of the most commonly used instruments are SCORAD and EASI.[61] Worsening disease severity may result from patients and/or family members applying an inadequate amount of drug to targeted treatment sites, which can be related to steroid phobia, improper technique, or the daily burden of disease. Data suggest that families spend an average of 63 minutes per day managing their child's AD, including time applying topical treatments and avoiding triggers.[62] As a result, it is important that pharmacists revisit the FTU reference tool at follow-up visits, demonstrate the recommended amount of drug that is required based on body surface area affected, and emphasize the importance of daily adherence to written action plans. When behavioral- or disease-related support beyond pharmacist-provided education is needed, consideration for physician referral is appropriate.

Conclusion

Several conventional therapies as well as 2 first-in-class agents are available to treat AD disease flares and extend periods of remission. Data show that no single treatment regimen will work for all patients. Consequently, treatment strategies must be individualized. The implementation of coordinated interprofessional care methods and a pharmacist-patient care process is critical to achieve optimal patient health and medication outcomes. Sufficient time must be spent providing patient education and teaching self-management strategies through the development of AD written action plans. By increasing patient education efforts, reviewing evidence-based methods to treat disease, and addressing unfounded concerns about new and existing therapies, medication adherence may improve while reducing unnecessary costs associated with the management of AD.

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FIGURE. American Academy of Dermatology Eczema Action Plan[58]

Eczema Action Plan

Eczema under control

Skin soft, supple, maybe some dryness

1. Bathe (5-10 minutes) in lukewarm water every _____ .
2. Apply moisturizer to all skin within 3 minutes of finishing bath.
3. Apply moisturizer **2 more times** during day to skin that feels dry or often flares.

Eczema flare

Itchy skin with redness or rash

Use your child's medicine and moisturizer (shown below) as often as indicated.

Bathe your child (5-10 minutes) in lukewarm water every _____.

Within 3 minutes of bathing:

- Apply child's medicine (shown below) to the eczema.
- Apply child's moisturizer, skipping areas with medicine. You don't want to apply moisturizer on top of the medicine.

Medicine for mild flare (*redness, some itch*)

Face _____ Apply _____ times a day (maximum _____ days)

Scalp _____ Apply _____ times a day (maximum _____ days)

Body _____ Apply _____ times a day (maximum _____ days)

Medicine for moderate or severe flare (*very itchy rash*)

Face _____ Apply _____ times a day (maximum _____ days)

Scalp _____ Apply _____ times a day (maximum _____ days)

Body _____ Apply _____ times a day (maximum _____ days)

Cleanser

_____ Use _____ times a day

Moisturizer

Day _____ Apply _____ times a day

Night _____

Other medicine

Itching (*day*)
Take _____ tsp/cc/pills of _____ in the morning.

Itching (*night*)
Take _____ tsp/cc/pills of _____ before bed.

Skin
Take _____ tsp/cc/pills of _____ for ____ days,
taking ____ times per day.

When to call the dermatologist

- Skin weeping, oozing pus
- Skin very painful
- Severe itch
- Fever
- Chills
- Eczema remains the same or barely diminishes with treatment

If your child has a **fever and clusters of itchy blisters**, call your dermatologist immediately. If you cannot reach your dermatologist, take your child to the nearest emergency room.

Dermatologist _____

Phone _____

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