Chapter 119: Atopic Dermatitis

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UPDATE SUMMARY

Update Summary

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The following sections were updated:

- Clarified use of JAK inhibitors for moderate-to-severe atopic dermatitis
- Added discussion of tralokinumab place in therapy, appropriate dosing, side effects, and monitoring
- Updated references

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 16, Dermatologic Drug Reactions and Common Skin Conditions.

KEY CONCEPTS

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1. Atopic dermatitis is a chronic skin disorder involving inflammation associated with intense pruritus (itching), a hallmark symptom. Management of atopic dermatitis must always include appropriate management of the associated pruritus.

2. Atopic dermatitis is associated with other atopic diseases such as asthma and allergic rhinitis in the same patient or family. The three conditions are known as the *atopic triad*.

3. The prevalence of atopic dermatitis has increased two- to threefold in many developed and developing countries during the past three decades. Age and country or regional differences, with some countries, show no change or even a decrease. Rural areas have lower prevalence rates.

4. There are genetic and environmental factors in the pathogenesis and pathophysiologic manifestations of atopic dermatitis. The inheritance pattern is not straightforward. More than one gene may be involved in the disease, with the filaggrin gene (*FLG*) being a key player. Other genes coding for specific cytokines are also involved.

5. Atopic dermatitis usually presents in infants and young children. The clinical presentation differs somewhat depending on the age of the patient.

6. Disease severity can be determined by using SCORAD (Severity Scoring of Atopic Dermatitis). This composite index assesses both signs and symptoms to classify overall disease severity as mild, moderate, or severe, which is useful in determining appropriate treatment approach.

7. Secondary bacterial skin infections are common in patients with atopic dermatitis and must be promptly treated.

8. Management of atopic dermatitis must always include appropriate nonpharmacologic management of any controllable environmental factors, such as avoidance of identified triggers. These may include aeroallergens (eg, mold, grass, pollen), foods (eg, peanuts, eggs, tomatoes), chemicals (eg, detergents, soaps), clothing material (eg, wool, polyester), temperature (eg, excessive heat), and humidity (eg, low humidity).

9. Nonpharmacologic management of atopic dermatitis entails managing the symptoms associated with pruritus and encouraging appropriate skin care habits such as proper bathing techniques and the copious use of moisturizers, which is a standard of care.

10. Topical corticosteroids (TCS) are the drugs of first choice for atopic dermatitis.

11. Topical calcineurin inhibitors (TCI), that is, tacrolimus and pimecrolimus, are alternate treatment options for adults and children over the age of 2 years.

12. Phototherapy is a second-line treatment when TCS and TCI fail.

13. Biologic agents and JAK inhibitors may be an option for moderate-to-severe atopic dermatitis in adults and adolescents (not approved in children).

14. This chronic illness has substantial socioeconomic impact. The burden of disease is significant, and the societal cost is magnified by undertreatment.

BEYOND THE BOOK

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Some of the treatment modalities for atopic dermatitis are also used in psoriasis. Review the discussion about topical corticosteroids (including the corticosteroid potency chart) in Chapter 118, "Psoriasis," in this textbook.

INTRODUCTION

1 Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease. It is often referred to as *eczema*, which is a general term for several types of skin inflammation. AD is the most common type of eczema (Table 119-1).[1] Pruritus is the hallmark symptom and presentation and is responsible for much of the disease burden borne by patients and their families.[2]

TABLE 119-1

Types of Eczema (Dermatitis)

- **Allergic contact eczema (dermatitis):** A red, itchy, weepy reaction where the skin has come into contact with a substance that the immune system recognizes as foreign, such as poison ivy or certain preservatives in creams and lotions.
- **Atopic dermatitis:** A chronic skin disease characterized by itchy, inflamed skin.
- **Contact eczema (dermatitis):** A localized reaction that includes redness, itching, and burning where the skin has come into contact with an allergen (an allergy-causing substance) or with an irritant such as an acid, cleaning agent, or other chemical.
- **Dyshidrotic eczema:** Irritation of the skin on the palms of hands and soles of the feet characterized by clear, deep blisters that itch and burn.
- **Neurodermatitis:** Scaly patches of the skin on the head, lower legs, wrists, or forearms caused by a localized itch (such as an insect bite) that become intensely irritated when scratched.
- **Nummular eczema:** Coin-shaped patches of irritated skin—most common on the arms, back, buttocks, and lower legs—that may be crusted, scaling, and extremely itchy.
- **Seborrheic eczema:** Yellowish, oily, scaly patches of skin on the scalp, face, and occasionally other parts of the body.
- **Stasis dermatitis:** A skin irritation on the lower legs, generally related to circulatory problems.

Data from Reference 1.

2 This form of dermatitis is commonly associated with a personal or family history of other atopic disorders, such as allergic rhinitis and asthma[2] (collectively known as the *atopic triad*). AD has been considered the start of the "atopic march"[2]; however, the association with other atopic conditions is multifactorial and complex since this progression does not happen in all cases.[2] The disease can have periods of exacerbation, or flare-ups, followed by periods of remission. These flare-ups may be disruptive to the patient's quality of life and may affect the entire family. Disease flare-ups may be difficult to manage and may be complicated by secondary infections. About one-half (estimate up to 65%) of cases in children first manifest before the age of 1 year[1-4]; these cases are termed *early onset atopic dermatitis*.[3,5] Onset of AD is most common between 3 and 6 months of age.[2] Approximately 85% to 90% of patients develop symptoms before the age of 5 years.[2]

About 10% to 30% of children with AD will have the same skin condition continuing into their adulthood.[2] Early and severe onset, family history of AD, and early allergen sensitizations are risk factors for a prolonged course.[3] Furthermore, patients who have apparently outgrown their disease may continue to have sensitive hyper-reactive skin and might have recurrences after long symptom-free periods.[3] However, onset after the age of 30 years is much less common and is often caused by exposure to harsh or wet conditions[1] such as repeated skin trauma or exposure to harsh chemicals.

EPIDEMIOLOGY

3 The prevalence of AD is generally said to have increased two- to threefold in developed and developing countries during the past three decades.[5] In

developed countries, an estimated 15% to 30% of children and 2% to 10% of adults are affected.[3,5,6] The prevalence has increased worldwide, as earlier prevalence rates were estimated at 10% to 15% in children.[4] In developed countries, the lifetime prevalence seems to have plateaued at 10% to 20%, whereas in many developing countries, the lifetime prevalence may be lower but continues to increase.[3]

3 The largest international study of the prevalence of AD found both age and country differences in prevalence rates.[7] This was the International Study of Asthma and Allergies in Childhood (ISAAC), which was conducted in three phases.[8] The strength of this study was the use of a uniformly validated methodology that allowed a direct comparison of results from pediatric populations worldwide.[9] ISAAC Phase One included 700,000 children from 156 centers in 56 countries between 1992 and 1998. ISAAC Phase Two studied allergic causes from 30 centers in 22 countries. ISAAC Phase Three repeated a multicountry cross-sectional survey (1999–2004) and included 187,943 children aged 6 to 7 years from 64 centers in 35 countries and 302,159 adolescents aged 13 to 14 years from 105 centers in 55 countries. For children aged 6 to 7 years, most countries showed an increase of two standard deviations (SDs) in mean annual prevalence over a 5- to 10-year period. In contrast, for adolescents aged 13 to 14 years, the trends differ from country to country. Large increases in prevalence were seen in developing countries (eg, Mexico, Chile, Kenya, and Algeria, and seven countries in Southeast Asia). But in other countries with formerly high prevalences, the mean annual prevalence in eczema symptoms has either leveled off or decreased. Most of the largest decreases (SD ≥2) in prevalence were reported from developed countries in northwest Europe (eg, the United Kingdom, Ireland, Sweden, Germany) and New Zealand.[7] The ISAAC study has suggested that a maximum prevalence plateau of approximately 20% has emerged.[7,8]

There were no differences according to the sex of the study participant, or with gross national income at a country level.[7] This is consistent with other reports that AD affects males and females at approximately the same rate.[1] There is a lower prevalence of AD in rural areas when compared with urban areas,[2] suggesting a link to the *hygiene hypothesis*,[10,11] which postulates that the absence of early childhood exposure to infectious agents increases susceptibility to allergic diseases.[10-12] In contrast, children attending daycare centers before 3 months of age have less atopy and asthma in later childhood,[11,12] and areas with diffuse and chronic helminth infestations have a low prevalence of allergic diseases.[12] In addition, a European birth cohort study involving 1,133 newborns showed that children born to farm families had a lower prevalence of sensitization to seasonal inhaled allergens such as grass pollen.[11,13] Maternal exposure during pregnancy (ie, prenatal exposure) to animal sheds correlated with the lower prevalence rate in the farm children. However, there were no differences in prevalence related to inhaled perennial allergens. Parasitic infections decreased the risk of allergen sensitization.[11] A systematic review reported that exposures to endotoxin, farm animals, and dogs may protect against AD.[14]

Reported risk factors associated with higher prevalence include urban environment, higher socioeconomic status, higher level of family education, a family history of AD, female gender (after age 6 years), and smaller family size.[8] However, more recent studies are conflicting. There are no consistent findings that higher socioeconomic status or male/female gender affect the risk of AD.[2] Urban living does increase the risk of AD, but studies attempting to identify causative environmental agents have been inconclusive.[2] Strongly associated risk factors include a family history of AD, and functional mutations in the *FLG* gene.[2]

ETIOLOGY

4 AD is a complex genetic disease that arises from gene-gene and gene-environment interactions. There are two major groups of genes involved. First, there are the genes encoding for epidermal or other epithelial structural proteins. Second, there are genes encoding for the major elements of the immune system.[5] However, the diagnosis of AD remains clinical, as there is no reliable biomarker to distinguish AD from other inflammatory conditions.[15]

The inheritance pattern is not straightforward. More than one gene is likely involved in the disease. There is an increased risk for a child to have AD if there is a family history of other atopic diseases, such as hay fever or asthma. The risk of AD is two- to threefold higher in children with one atopic parent and three- to fivefold higher if both parents are atopic.[2] Studies of identical twins show that a person whose identical twin has AD is seven times more likely to have AD than someone in the general population.[1] And a person whose fraternal twin has AD is three times more likely to have AD than someone in the general population.[1] Another estimate is 80% concordance in monozygous twins and 20% in heterozygous twins.[10]

Thus, genetic predispositions to developing AD exist. There is a genetic predisposition in patients with atopy to demonstrate T-helper (Th_2) predominance—hence increased Th_2 cell activity.[3] At least 32 susceptibility loci have been identified through gene-mapping studies, but they explain less than 20% of the estimated heritability.[3] The strongest known genetic risk factor for AD is null mutations in filaggrin (FLG).[3] The filaggrin gene (*FLG*) on chromosome 1q21.3 encodes for a key structural protein in epidermal differentiation.[3] FLG mutations also cause the semidominant skin-scaling disorder ichthyosis vulgaris, characterized by abnormal skin dryness and palmer hyperlinearity, which are features often found in AD.[3] More specifically, there are several possible genes on the chromosomes 3q21, 1q21, 16q, 17q25, 20p, and 3p26. Of these chromosomes, 1q21 has the highest linkage region. This region has a family of epithelium-related genes called the epidermal differentiation complex.[5] One of these genes is the *FLG*, on chromosome 1q21.3, which encodes for profilaggrin that degrades to filaggrin proteins.[2] Filaggrin proteins play key roles in epidermal differentiation, including terminal differentiation of the epidermis and formation of the skin barrier (including the stratum corneum).[2,16] Filaggrin breakdown products are natural moisturizers and contribute to epidermal hydration and barrier function.[2] Mutations or deficiency of *FLG* result in an abnormality in permeability barrier function.[16] Patients with AD who carry FLG mutations have more persistent disease, a higher incidence of skin infections with herpes virus (eczema herpeticum) and a greater risk for multiple allergies.[16] However, FLG mutation is neither necessary nor sufficient to cause AD. Up to 60% of carriers will not develop AD, and many patients with AD do not carry an FLG mutation.[3]

Epidermal barrier dysfunction is a prerequisite for the penetration of high-molecular-weight allergens in pollens, house dust mite products, microbes, and food.[5] In mice studies, this barrier abnormality lowers irritability thresholds, and enhanced cutaneous allergen penetration.[16] In humans, two common FLG variants (*R501X* and *2282de14*) with an estimated combined allele frequency of about 6% have been identified in individuals of European descent.[17] Eighteen other less common variants have also been identified in Europeans, with an additional 17 mutations restricted to individuals of Asian descent.[17] Each of these variants leads to nonsense mutations that either prevent or severely diminish the production of filaggrin in the epidermis.[17] Mutations of FLG occur mainly in patients with early onset AD and may be associated with the development of asthma in patients with AD.[5,17] However, FLG mutations are identified in only 30% of European patients with AD, implying that other genetic mutations affecting other epidermal structures may be important (eg, changes in the cornified envelope proteins involucrin and loricrin, or lipid composition).[5]

There are other genes encoding for the immune system that may be associated with AD, especially those on chromosome 5q31-33.[5] These genes code for cytokines that regulate IgE synthesis. Cytokines are produced by helper T cells (TH_0, TH_1, TH_2, TH_3).[11] T-helper type 1 (TH_1) cells produce cytokines that suppress immunoglobulin E (IgE) production (eg, interferon-γ and interleukin-12 [IL-12]).[5] T-helper type 2 (TH_2) cells produce cytokines that increase IgE production (eg, IL-5 and IL-13).[5,18] In patients with AD, there is an imbalance between TH_1 and TH_2 immune responses. These patients are genetically predisposed to TH_2 predominance, seen as increased TH_2 cell activity.[2,5,9,18] Increased TH_2 activity causes the release of IL-3, IL-4, IL-5, IL-10, and IL-13, resulting in blood eosinophilia, increased total serum IgE, and increased growth and development of mast cells.[2,5,11,18] This is seen in the initial and acute phase of AD.[9] In addition, these cytokines affect the maturation of B cells and cause a genomic rearrangement in these cells that favors isotype class switching from immunoglobulin M (IgM) to IgE.[5] As discussed below, epidermal Langerhans cells (LCs) and dendritic cells (DCs) with high-affinity IgE receptors uptake allergens and mediate the inflammatory response.[11]

In summary, FLG deficiency alone can provoke a barrier abnormality in the epidermis and predispose to the development of AD by enhancing allergen absorption through the skin.[19] Furthermore, there is complex relationships, including genetic and nongenetic risk factors, that modify an individual's susceptibility to allergic disease.[20] Complex genetic factors contribute to the increased susceptibility to AD (FLG mutations and gene-gene interactions). These, along with environmental factors such as food allergens[21] (gene-environment interactions), result in the pathophysiologic changes and clinical presentations associated with AD.

PATHOPHYSIOLOGY

The initial mechanisms that trigger inflammatory changes in the skin in patients with AD are unknown. Neuropeptides, irritation, or pruritus-induced scratching may be causing the release of proinflammatory cytokines from keratinocytes. Alternatively, allergens in the epidermal barrier or in

food[21] may cause T-cell mediated but IgE-independent reactions. Allergen-specific IgE is not a prerequisite.[5] Characteristic features in pathophysiology are skin barrier dysfunction and immune deviation toward TH_2 with subsequent increased IgE.[10] The disease is further complicated by microbial colonization with pathologic organisms resulting in increased susceptibility for skin infections.[10]

As discussed above, skin barrier dysfunction plays a critical role in the development of AD,[10,11,16,22] with loss of function mutations in *filaggrin* being a major risk factor.[16,22] Other factors may include a deficiency of skin barrier proteins, increased peptidase activity, lack of certain protease inhibitors, and lipid abnormalities.[22] There must be epidermal barrier dysfunction for high-molecular-weight allergens in pollens, house dust mite particles, microbes, and foods to penetrate the skin barrier. Atopic skin has reduced antimicrobial peptides (AMPs). AMPs are normally produced by keratinocytes, sebocytes, and mast cells, and they form a chemical shield on the surface of the skin. Reduced AMPs result in a diminished antimicrobial barrier, which correlates with increased susceptibility to infections and superinfections seen in these patients.[23]

Upon penetration of the epidermal barrier, allergens are met by DCs. DCs are antigen-presenting cells populating the skin, respiratory tract, and mucosa of the GI tract (ie, at the front line of pathogen entry).[24] DCs then enhance TH_2 polarization, resulting in increased production of IgE. Keratinocytes in the skin of patients with AD also produce high levels of an IL-7–like protein, which again drives DCs to enhance TH_2 polarization. Epidermal DCs in patients with AD bear IgE and express its high-affinity receptor (FcεRI).[25-27] Total serum IgE is often elevated in patients with AD,[1,2] especially during an exacerbation.

However, on initial presentation, patients with early onset AD generally do not have increased total serum IgE levels (ie, there is no detectable IgE-mediated allergic sensitization). IgE-mediated allergic sensitization may occur several weeks or months after the initial AD lesions, although in some children—mostly girls—this sensitization never occurs.[5] Furthermore, elevated total serum IgE is not specific to AD and can be associated even with nonatopic conditions.[2]

Other potential biomarkers discovered include serum CD30, macrophage-derived chemoattractant (MDC), interleukins (IL)-12, -16, -18, and -31, and thymus and activation-regulated chemokine (TARC); however, to date none of them have shown reliable sensitivity nor specificity for clinical use.[2]

Predisposing Factors

Several factors can predispose patients to development of AD. These include climate, infection, genetics, environmental aeroallergens, urban versus rural living, breastfeeding and time of weaning, obesity, pollution/tobacco smoke, and food/diet. A Western diet with high amounts of sugar and polyunsaturated fatty acids, a small family size, a high education level in the household, living in urban settings, and living in regions with low exposure to UV radiation and low humidity are all factors that may increase the risk of AD.[3]

Hot and extremely cold climates are both poorly tolerated by patients with AD. Dry weather, common in the winter, causes increased skin dryness. Hot weather causes increased sweating, resulting in pruritus.

Patients with AD are commonly colonized by *Staphylococcus aureus* bacteria. Clinical infections with *S. aureus* frequently cause flare-ups of AD.

As discussed previously, genetics plays a role in AD. Family history of AD is a strong risk factor.

Exposure to environmental aeroallergens is another risk factor. Dust mites, pollens, molds, cigarette smoke, and dander from animal hair or skin may worsen the symptoms of AD.[13]

The role of food as antigens in the pathogenesis of AD is still not fully understood.[3,21] Preliminary results (mostly animal studies) indicate that defects in the skin and gut barrier function may facilitate sensitization to food allergens.[21] Small amounts of environmental foods (low-dose exposure from foods on tabletops, hands, dust) may penetrate the skin barrier and be taken up by LCs, leading to TH_2 responses and IgE production.[28] However, early high-dose oral food consumption induces oral tolerance. The timing and balance of cutaneous and oral exposure determines whether a child will have allergy or tolerance.[28] Increased serum IgE antibodies to a particular food is evidence of sensitization to a food and is consistent with—although not proof of—a food allergy.[1,29] Eczema may frequently be a manifestation of food allergy,[28] and patients with AD have a higher prevalence of food allergy

than those in the general population.[1] Conversely, there is a belief that food allergy may be caused by AD, and in most patients with coexisting AD and food allergy, AD precedes the food allergy. (The assumption is that AD is a causal risk factor for asthma and systemic allergen sensitization in the context of FLG mutations.[16]) Regardless, the two conditions coexist, and the likelihood of an infant or child with AD also having food allergy or other allergies must be kept in mind.[29]

There is a known epidermal barrier dysfunction in AD, allowing for increased low-level skin permeability to allergenic foods. Certain foods may trigger acute reactions including urticaria and anaphylaxis. The most commonly reported allergenic foods are hen's eggs, cow's milk, peanuts, wheat, soy, tree nuts, shellfish, and fish.[1,30] Individual food allergies, such as peanut allergy, have increased in prevalence in the past decade[28,29]; new food allergies may also be increasing in prevalence, particularly kiwi allergy[28,31] and sesame seed allergy.[28,32] Allergies to seafood, peanuts, and tree nuts are more likely to persist into adulthood, while allergies to cow's milk, hen's eggs, wheat, and soy generally resolve by late-childhood.[21] Consistent with the oral tolerance concept, early results from recent studies using sublingual and oral immunotherapy to specific food allergens (eg, cow's milk or peanut) indicate that it may be possible to induce oral tolerance, and that it may be possible to desensitize children to some allergenic foods.[33] Nine to 12 months of immunotherapy were needed to observe the beneficial effect and "the present evidence does not warrant routine recommendation" by the AAD.[34] Injectable allergen-specific immunotherapy is also being studied.[34] National Institute of Allergy and Infectious Diseases (NIAID) suggests limited food allergy testing (ie, cow's milk, eggs, wheat, soy, peanut) if a child <5 years old has moderate-to-severe AD and persistent disease despite optimal therapy.[29,34] For more information about management of food allergies the reader is directed to the 2010 NIAID-sponsored expert panel's report, available at www.niaid.nih.gov.[29]

CLINICAL PRESENTATION

Diagnosis of AD is generally based on clinical presentation (Table 119-2).[1] There is no objective diagnostic test or reliable biomarker for the clinical confirmation of AD.[1-3] On occasion, skin biopsy specimens or other tests (eg, total and/or allergen-specific serum IgE, potassium hydroxide preparation, patch testing, and/or genetic testing) may be used to rule out other or associated skin conditions.[2] *Filaggrin* gene mutations may be associated with persistent and more severe AD as well as early onset cases.[22]

TABLE 119-2

Skin Features Associated with Atopic Dermatitis

- **Atopic pleat (Dennie–Morgan fold):** An extra fold of skin that develops under the eye.
- **Headlight sign:** Sparing of the skin on top of the nose.
- **Herthoge's sign:** Thinning or absence of the lateral portions of the eyebrows.
- **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.

Atopic dermatitis follows a relapsing course.[34,35] Studies reviewing the natural course of the disease usually describe the disease pattern as persistent, intermittent, or in remission.[8] A 2004 study found that 43% were in complete remission after the age of 2 years, with 19% having persistent disease and 38% an intermittent pattern.[8]

The clinical presentation of AD differs depending on the age of the patient. In infancy, the earliest onset of AD usually occurs between 3 and 6

months of age, with 60% of patients developing symptoms within the first year of life, and 85% to 90% having developed symptoms before the age of 5 years.[1,2] The initial presentation in infancy is an erythematous, papular skin eruption that may first appear on the cheeks and chin as a patchy facial eruption which may progress to red, scaling, oozing skin.[1] The eruption shows a centrifugal distribution affecting the malar region of the cheeks, forehead, scalp, chin, and behind the ears while sparing the central areas (ie, the nose and paranasal creases). Sparing of the skin on top of the nose is a characteristic feature (known as the "headlight sign"), and there is thinning or absence of the lateral portions of the eyebrows (known as the Herthoge's sign).[3] Lesions occur in the flexor surfaces, such as antecubital and popliteal fossae. Over the next few weeks and as the infant becomes more mobile and begins crawling, the lesions spread to the extensors of the lower legs, and eventually the entire body may be involved, with sparing of the groin, axillary region, and the nose.[1,2,35] These lesions are associated with uncontrollable itchiness, and the infant will become irritable and may try to rub his or her face to relieve the itch. Scratching may occur quite early, and infants with AD may scratch themselves continuously, even during sleep.[2] Sleep disruption occurs in up to 60% of children with AD, increasing to 80% or more during exacerbations.[2] Excessive rubbing or scratching may result in excoriation and predispose the patient to secondary infections.

In childhood, the skin is often dry, flaky, rough, cracked, and may bleed because of scratching. With repeated scratching and rubbing, the skin becomes lichenified. Lichenification, usually localized to the flexural folds of the extremities, is characteristic of childhood AD in older children and in adults.[35] Lichenification signifies repeated rubbing of the skin and is seen mostly over the folds, bony protuberances, and forehead.[35] Excoriations and crusting are also commonly seen, along with secondary infections. Sometimes increased folds are seen underneath the eyes (so-called Dennie–Morgan folds).[35] Lesions are still most commonly seen in the flexor surfaces of the body, particularly the flexural creases of the antecubital and popliteal fossae.[35]

Sleep disturbances also occur. One study reported that there are both brief and longer awakenings associated with scratching episodes that affect sleep efficiency in school-age children with AD.[36]

In adulthood, lesions are more diffuse with underlying erythema. The face is commonly involved and may be dry and scaly. Lichenification may again be seen. A brown macular ring around the neck, representing a localized deposit of amyloid, is typical but not always present.[35]

In people of color, skin lesions may present in a different manner, often with a perifollicular distribution.

Although no objective diagnostic test confirms the presence of AD,[1,2] some signs, symptoms, and other factors are commonly used in its diagnosis. These include pruritus, early age of onset, eczematous skin lesions that vary with age, chronic and relapsing courses, dry and flaky skin, IgE reactivity, family or personal history of asthma or hay fever, or other atopic diseases (Tables 119-3 and 119-4).[2,35] Allergy skin testing has little utility in AD, although negative results may help rule out certain substances as triggers; however, positive results may be unrelated to disease activity, and false positives are common.[1]

TABLE 119-3

Clinical Features in the Diagnosis of Atopic Dermatitis

Essential Features (Must Be Present):

- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns
    - Facial, neck, external involvement (infants, children)
    - Flexural lesions (any age group)
    - Sparing of groin and axillary regions
  - Chronic or relapsing history

Important Features (Seen in Most Cases, Supports the Diagnosis of AD):

- Early age of onset
- Atopy
  - Personal/family history
  - IgE reactivity
- Xerosis

Data from Reference 2.

TABLE 119-4

Major and Minor Signs and Symptoms of Atopic Dermatitis

Major Indicators

- Pruritus (intense itching)
- Characteristic rash in locations typical of the disease
- Chronic or repeatedly occurring symptoms
- Personal or family history of atopic disorders (eczema, hay fever, asthma)

Selected Minor Indicators

- Early age of onset
- Dry skin that may also have patchy scales or rough bumps
- Increased serum IgE
- Numerous skin creases on the palms
- Hand or foot involvement
- Inflammation around the lips
- Nipple eczema
- Susceptibility to skin infection
- Positive allergy skin tests

Data from Reference 1.

1 Pruritus is a quintessential feature of AD, and a diagnosis cannot be made if there is no history of itching.[1-4,35] Scratching and rubbing itchy atopic skin further irritates the skin, increases inflammation, and exacerbates itchiness.[3] Atopic skin can itch during sleep. This nighttime itching is a problem

for many infants and children with the disease, since there is no conscious control of scratching during sleep.[1,2] Pruritus is the symptom that most affects the health-related quality of life for most patients with AD. In studies, more than 50% of patients rated their pruritus as bothersome or extremely bothersome and reported that they often or always experienced intolerable symptoms.[35]

Pruritus can be triggered by a variety of factors. The most common triggers of itch have been reported as heat and perspiration (96%), wool (91%), emotional stress (81%), certain (usually vasodilatory) foods (49%), alcohol (44%), upper respiratory infections (36%), and house dust mites (>35%).[35,36]

Once pruritus occurs, the surrounding normally nonpruritic skin area (whether inflamed or noninflamed) may be sensitive and react to light stimuli and begin itching (a process known as *allokinesis*). Allokinesis is typical of AD.[35,36] As a result of allokinesis, patients with AD may experience pruritic attacks when their skin is touched accidentally by mechanical factors such as clothing, especially wool products.[36]

Elevated serum IgE may be seen, consistent with the genetically predetermined dominance of TH_2 cytokines causing increased IgE. In addition, increased serum IgE antibodies to a particular food, consistent with a food allergy, is common in patients with AD. Serum-based tests for allergen-specific IgE (formerly a radioallergosorbent test referred to as RAST) are used to screen for allergy to a specific substance or substances.[34] (Most labs use large autoanalyzers that rely on fluorescent or chemiluminesent labels rather than radiolabels to identify reactions, so RAST does not describe the technique used.) In some cases, allergen-specific IgE tests may be used to monitor immunotherapy or to see if a child has outgrown a specific allergy. The negative predictive value is high (>95%) but the specificity and positive predictive value are low (40%-60%).[34] Negative results help to rule out a food allergy, whereas positive (elevated) allergen-specific IgE test results only signify sensitization and require clinical correlation and confirmation.[34] The level of IgE may not correlate with the severity of an allergic reaction or with the severity of AD.

With respect to IgE reactivity, several candidate genes that encode cytokines involved in the regulation of IgE synthesis have been identified, notably on chromosome 5q31-33.[2] Increased Th_2 activity leads to release of IL-3, IL-4, IL-5, IL-10, and IL-13, which causes eosinophilia, increases IgE, and increases the growth and development of mast cells.[35] In addition to eosinophils and mast cells, basophils and newly identified innate immune cells called group 2 innate lymphoid cells (ILC2s) have been shown to underlie the pathogenesis of AD.[35] The above cytokines also affect B-cell maturation, causing a genomic rearrangement that favors isotype class switching from IgM to IgE.[2] Th_{17} cells have been found to be elevated, with its role not yet clearly defined.[35]

A clinically useful set of criteria for the diagnosis of AD is as follows: atopy, pruritus, eczema, and altered vascular reactivity.

Disease Severity

6 Disease severity can be classified as mild, moderate, or severe. Assessing the severity of AD includes subjective symptoms and objective signs—in particular, the subjective evaluations relating to pruritus and sleep disturbance are particularly important. Composite scores assessing both signs and symptoms must be used to assess overall disease severity.[36] SCORAD (Scoring of Atopic Dermatitis) is a composite score developed by the European Task Force of Atopic Dermatitis (ETFAD), where a SCORAD score >50 defines severe AD, and one <25 considered mild AD.[36] There is also a Patient-Oriented SCORAD (PO-SCORAD) which is also useful since it can be administered independent of the physician; and the PO-SCORAD correlates well with SCORAD.[36] In addition, there is an objective assessment tool for visible lesions called EASI (Eczema Area and Severity Score) which is often used together with a subjective symptom assessment tool called POEM (Patient-Oriented Eczema Measures); this pair of tests is especially useful in the clinical trial setting.[36] Both SCORAD and PO-SCORAD are available as apps from the Eczema Foundation at https://www.fondation-dermatite-atopique.org/en/healthcare-professionals-space (Fig. 119-1).

FIGURE 119-1

Example of use of SCORAD tool for atopic dermatitis disease severity assessment. A composite score of 40.8 would be consistent with moderate disease. *(SCORAD and PO-SCORAD copyright © Pr JF Stalder, Eczema Foundation, 2020. Reprinted with permission.)*

PO-SCORAD on Day _____

Last name: _____ First name: _____

Date of birth: _____ Today's date: _____

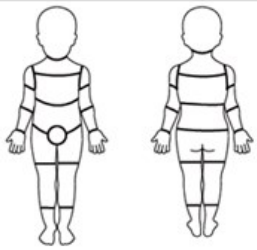
Who is filling out this questionnaire?

- ❍ The patient
- ❍ The patient's mother
- ❍ The patient's brother / sister
- ❍ The patient, assisted by a parent
- ❍ The patient's father
- ❍ Other (please specify) _____

Surface affected

- ❍ patient under 2 years old
- ❍ patient over 2 years old

Using the drawing provided, shade the areas affected by eczema.



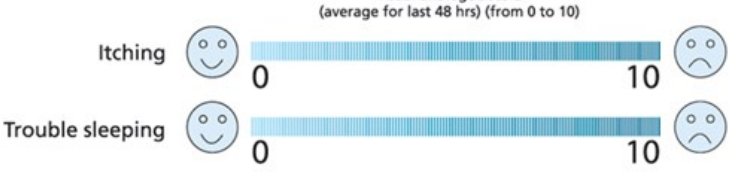
Intensity of symptoms

Criteria	Intensity (from 0 to 3)
Dryness*	
Redness	
Swelling	
Oozing/scabs	
Scratch marks	
Thickening of skin	

* Dryness is evaluated on the skin not affected by eczema.

Subjective symptoms: itching + trouble sleeping

visual analogue scale
(average for last 48 hrs) (from 0 to 10)



You can download a free application that will help you calculate the PO SCORAD automatically. Your computer will create a curve as your eczema evolves and you can print it and give it to your doctor.

Today's PO SCORAD:

Please visit: PoScorad sur Google play et Apple store
www.opened-dermatology.com
ou www.fondation-dermatite-atopique.org

Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Complications

Patients with AD are prone to skin infections. Atopic skin is drier and the stratum corneum has weakened protective abilities; combined with the abnormal skin barrier function and immune defense, there is an increased risk of secondary bacterial skin infections with staphylococci or streptococci, and viral infections such as herpes simplex or even fungal infections.[1,2] Constant scratching to relieve pruritus may cause excoriations, further compromising the integrity of the skin barrier. *S. aureus* is a common cause of secondary bacterial infections in AD.[3,10] Binding of *S. aureus* is enhanced by skin inflammation as seen in AD. Many patients with AD are colonized with *S. aureus* and may have exacerbations after skin infections of this organism.[10] Secondary bacterial infections may present as yellowish crusty lesions and should be promptly treated. Oral (systemic) antibiotics are generally more effective than topical treatment.[1]

Patients with AD are also more prone to disseminated infections with herpes simplex or vaccinia virus. Severe viral infections such as eczema herpeticum or eczema vaccinatum might be linked to the severity of atopy. Eczema herpeticum is a severe widespread skin infection with herpes simplex virus (HSV) that occurs in up to 3% of patients, in particular those with severe disease.[3] *Molluscum contagiosum* virus infection may be seen in children and adolescents with AD.[3] Smallpox vaccination is contraindicated in patients with AD.

TREATMENT

Desired Outcomes

In treating patients with AD, clinicians generally have the following clinical goals in mind:

1. Provide symptomatic relief—control the itching.
2. Control the AD.
3. Identify and, when possible, eliminate triggers and environmental aeroallergens.
4. Identify and minimize predisposing factors for exacerbations including any stressors.
5. Prevent future exacerbations.
6. Provide any social and psychological support needed for the patient, family, and caregivers.
7. Minimize or prevent adverse events from medications and other treatment modalities.
8. Treat to cure any secondary skin infections, if present.

Successful management of AD should include not only clearance of skin lesions, which may take days to weeks depending on the severity of disease—and this determines the type of treatment regimen—but also controls of the itch, minimizing or eliminating triggers, monitoring the patient to minimize or prevent adverse events from medications or other treatment modalities, and providing adequate social and psychological support for the patient, family, and caregivers.

The ultimate goal is to provide enough control of this chronic disease so that future exacerbations are prevented, thus ensuring that the patient's quality of life is minimally affected by AD. Because the course of the disease evolves over time, management strategies may change. Mild disease can be managed by reactive therapy, moderate-to-severe disease will require proactive therapy to maintain disease control.[36]

Both nonpharmacologic and pharmacologic therapies are important in managing the signs and symptoms of AD. Nonpharmacologic strategies include identifying and minimizing or eliminating preventable risk factors, such as known triggers and allergens, as well as appropriate skin care.[30,36]

Treatment guidelines and protocols for AD are available. These are listed in Table 119-5. At the time this chapter was prepared for publication, the American Academy of Dermatology (AAD) was updating its 2014 guidelines in a series of publications.[37] The reader is encouraged to access the online version of this chapter for updates.

TABLE 119-5

Useful Sources of Information About Treatment of Atopic Dermatitis

Published Guidelines or Treatment Protocols

- Davis DMR Drucker AM, Alikhan A et al. AAD guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Derm* 2022. Published pre-print Jan 24, 2022 https://doi.org/10.1016/j.jaad.2022.01.009
- Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I & part II. *J Eur Acad Dermatol Venereol* 2018;32(5):657–682 & 850-878.
- Wong ITY, Tsuyuki RT, Cresswell-Melville A, et al. Guidelines for the management of atopic dermatitis (eczema) for pharmacists. *Can Pharm J (Ott)* 2017;150(5):285-297.
- Gooderham M, Lynde CW, Papp K, et al. Review of systemic treatment options for adult atopic dermatitis. *J Cutan Med Surg* 2017;21(1):31-39.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol* 2014;70:338-351.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-132.
- Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:327-349.
- Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis. Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014; published online September 25, 2014. http://dx.doi.org/10.1016/j.jaad.2014.08.038.
- Eichenfield LF, Boguniewicz M, Simpson E, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics* 2015;136(3). http://www.pediatrics.org/cgi/doi/10.1542/peds.2014-3678.
- Rubel D, Thirumoorthy T, Soebaryo W, et al. Consensus guidelines for the management of atopic dermatitis: An Asia-Pacific perspective. *J Dermatol* 2013;40:160-171.
- Baron SE, Cohen SN, Archer CB. British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol* 2012;37(suppl 1):7-12.
- Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol* 2018;120:23-33.
- Simpson EL. Atopic dermatitis: A review of topical treatment options. *Curr Med Res Opin* 2010;26(3):633-640.
- Carbone A, Siu A, Patel R. Pediatric atopic dermatitis: A review of the medical management. *Ann Pharmacother* 2010;44:1448-1458.
- National Institute of Arthritis and Musculoskeletal and Skin Diseases. Handout on Health: Atopic Dermatitis. US Department of Health and Human Services. NIH Publication No. 09-4272. May 2013, www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp.
- Lynde C, Barber K, Claveau J, et al. Canadian practical guide for the treatment and management of atopic dermatitis. *J Cutan Med Surg* 2005;8 (suppl 5):1-9. http://www.springerlink.com/content/r5432000056r2748/fulltext.html.

Useful Websites

- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), US National Institutes of Health: http://www.niams.nih.gov/Health_Info/Atopic_Dermatitis/default.asp
- American Academy of Allergy Asthma & Immunology (AAAAI): http://www.aaaai.org/conditions-and-treatments/allergies/Skin-Allergy.
- American Academy of Dermatology: https://www.aad.org/education/clinical-guidelines, http://www.jaad.org/article/S0190-9622(13)01095-5/fulltext.
- DermNet NZ: http://dermnetnz.org/dermatitis/atopic.html.

Nonpharmacologic Therapy

8 9 Nonpharmacologic approaches to the treatment of infants and children with AD include the following[30,36,38]:

1. Apply moisturizers frequently throughout the day. Moisturizers are a standard of care for AD and there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.[30,36,38] Long-term moisturizer therapy improves AD associated xerosis.[36] Even stand-

alone use of moisturizers for 1 week improves mild-to-moderate AD flares.[39] Daily use of moisturizers from birth may reduce the development of AD in a high-risk population.[36,40]

2. Give lukewarm baths. There is insufficient evidence for patients with AD to recommend the addition of oils, emollients, or most other additives to bath water, or the use of acidic spring water.[38]
3. Apply moisturizer immediately after bathing. There is no standard for the frequency or duration of bathing appropriate for those with AD.[38]
4. Use nonsoap cleansers (which are neutral to low pH, hypoallergenic, fragrance free). Limited use.[38]
5. Use wet-wrap therapy (with or without TCS) during flare-ups for patients with moderate-to-severe AD. "Wet wrap" is applying damp tubular elasticized bandages and occlusive dressing to the limbs—this promotes skin hydration and absorption of emollients and TCS,[11] reducing disease severity and water loss.[11,38]
6. Keep child's fingernails filed short.
7. Select clothing made of soft cotton fabrics.
8. Consider using sedating antihistamines to reduce scratching at night.
9. Keep the child cool; avoid situations in which overheating occurs.
10. Learn to recognize skin infections and seek treatment promptly.
11. Attempt to distract the child with activities to keep him or her from scratching.
12. Identify and remove irritants and allergens.

Hydration is crucial, and adequate skin hydration is a fundamental part of managing AD.[30,36,38] Transepidermal water loss is greater in atopic skin than in normal skin. Thus, any measures to improve skin moisturization, such as liberal use of moisturizers, would be beneficial. Moisturizers are a standard of care and may be steroid sparing.[10,36,38] They are useful for both prevention and maintenance therapy.[10,38,41,42] They can be categorized based on their specific effects on the skin:

1. *Occlusives*: These agents provide an oily layer on the skin surface to slow transepidermal water loss, increasing the moisture content of the stratum corneum. These are the best moisturizers for patients with AD.
2. *Humectants*: In the stratum corneum, these agents increase the water-holding capacity. However, they are not useful in patients with AD because they have a stinging effect on open skin. Humectants act by drawing moisture from their surroundings to attract water to the skin surface. In humid environments, this works well; however, in dry and low humidity environments, humectants can draw water from deeper parts of the skin, thus further drying out the skin. Thus, they are not recommended for patients with AD.
3. *Emollients*: These agents smooth out the surface of the skin by filling the spaces with droplets of oil. As moisturizers, these are less effective than occlusives, but they can be useful in patients with AD.

However, note that the term "emollients" is often more broadly used to mean *all* nonmedicated moisturizers, including occlusives.[36] Nonmedicated "emollients" may also include active ingredients, softening the delineation of emollients from topical drugs.[36] The 2018 European consensus guideline defines *emollients* as "topical formulations with vehicle-type substances lacking active ingredients" and *emollients plus* as "topical formulations with vehicle-type substances and additional active, nonmedicated substances."[36] Usual ingredients in emollients can include mineral oil, petrolatum, and urea.[36] Emollient-plus products may contain active ingredients such as saponins, flavonoids, riboflavins from protein-free oat plantlet extracts, or bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis*.[36,43] These lysates both improve AD and positively influence the skin microbiome.[36,44] A cream based on *Aquaphilus dolomiae* extracts alleviates nonhistaminergic pruritus.[45] Ceramide-containing OTC moisturizers and prescription emollient devices (PEDs) with distinct ratios of lipids mimic endogenous compositions. However, to date these have not shown superiority

in AD.[38]

The humidity in the home should be kept at or above 50% and the room temperature kept on the cool side.[46]

Appropriate skin care is crucial in preventing flare-ups.[1] A daily skin care routine should include the following[46]:

1. Using scent-free moisturizers liberally as needed each day. Large quantities can be used.
2. Bathing in lukewarm water (never hot) for 5 to 10 minutes, once or twice daily.[30,36,38] Adding a capful of emulsifying oil[10] may help the body retain moisture; baths are better than showers. Bathing daily for 10 to 20 minutes may be desirable as long as a thick moisturizer is applied afterward. A 20-minute soak followed by immediate application of topical anti-inflammatory agents (eg, TCS) without towel drying is known as the "soak and smear" technique and is useful when the topical anti-inflammatory agent alone is inadequate.[38] Bathing twice daily during disease flares may also be a useful method for enhancing skin penetration of topical therapies and for debridement of crusting and staphylococcal colonization. The skin should be lightly towel dried (pat to dry, avoid rubbing or brisk drying).[1,46]
3. Scent-free moisturizer should then be applied while the skin is still moist or slightly damp (eg, within 3 minutes of towel drying).[46] Some fragrance-free moisturizers include Aveeno Baby Soothing Relief Moisture Cream, CeraVe lotion, Cetaphil, Neutrogena Hand Cream, and Vanicream products. Lotions may be used on the scalp and other hairy areas and for mild dryness on the face, trunk, and limbs; creams are more occlusive than lotions; ointments are the most occlusive and can be used for drier, thicker, or more scaly areas.[46]
4. Using nonsoap skin cleansers[1] may cause less skin irritation. Lipid- and fragrance-free skin cleansers may be particularly advantageous (eg, CeraVe facial cleansers [Foaming, Hydrating], CeraVe Eczema Body Wash, Cetaphil Gentle Skin Cleanser, Free and Clear Liquid Cleanser, Spectro Derm Cleanser, and Trisan Antibacterial Skin Cleanser). Aquanil, Dove, Neutrogena, and pHisoderm sensitive skin products have also been recommended as low-irritant products, and some are lipid free.
5. Avoiding alcohol-containing topical products including lotions, swabs, and wipes, as they may be drying.
6. Clothing should be double-rinsed. Mild detergents should be used to wash clothing, with no bleach or fabric softener.

PATIENT CARE PROCESS

Patient Care Process for Atopic Dermatitis

Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family)

- Patient/caregiver description of history of atopic dermatitis, subjective complaints of itch and other symptoms
- Signs associated with severity of itch (eg, excoriations, sleep disturbances)
- Signs associated with severity of atopic dermatitis (eg, areas of involvement)
- Signs of secondary skin infections
- Signs of caregiver stress or distress

Assess

- Severity of atopic dermatitis—classify into mild, moderate, or severe disease (eg, using SCORAD)
- Severity of itch
- Ability/willingness to pay for medical treatment options
- Emotional/psychological concerns (for patient and caregiver, if any)

Plan*

- Determine an appropriate treatment approach, that is, proactive versus reactive therapy
- Recommend the most appropriate therapies (nonpharmacologic and pharmacologic) for atopic dermatitis and itch
- Recommend the most appropriate treatment (treat to cure) and ongoing preventative strategies for secondary skin infection, if present
- Recommend management strategies for caregiver stress or distress, if needed

Implement

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Provide information about prevention of future flare-ups

Follow-up: Monitor and Evaluate

- Contact patient/caregiver in 1 to 2 weeks to follow up about the efficacy of recommended therapies and any issues with the treatment regimen
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed)
- Reinforce preventive measures including continuation of proactive therapy, if implemented
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a dermatologist, psychologist)

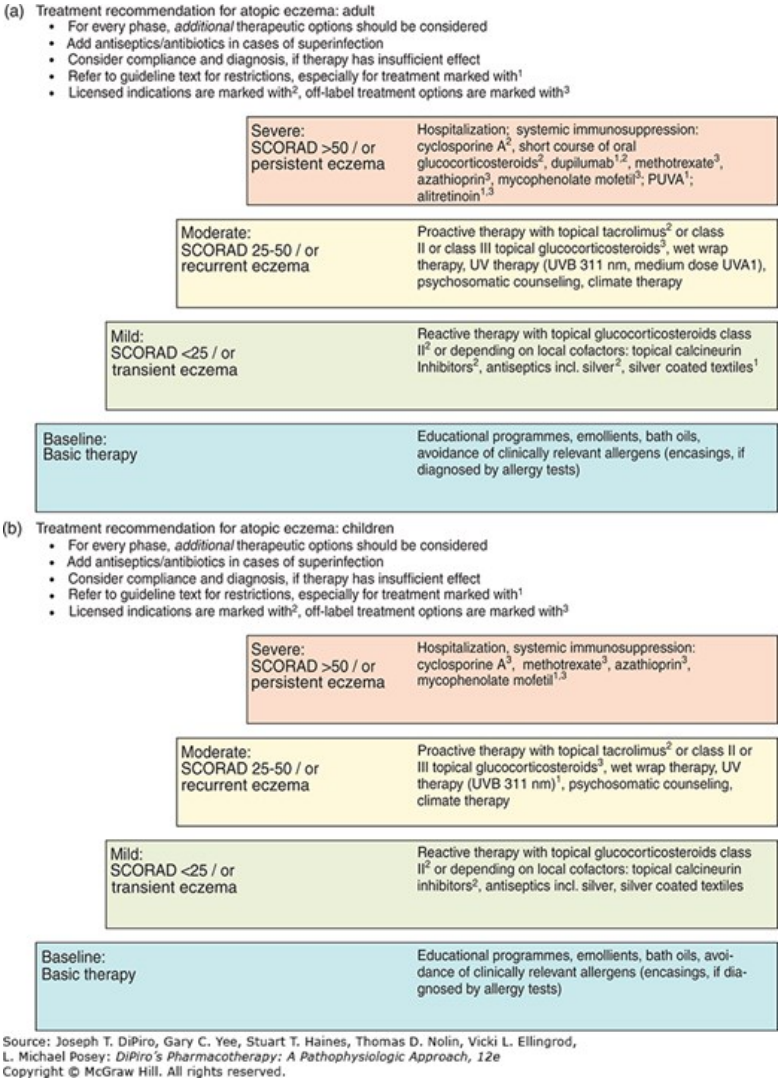
**Collaborate with patient, caregivers, and other healthcare professionals.*

Pharmacologic Therapy

Current treatment recommendations are based on disease severity, with reactive therapy appropriate for mild disease, and proactive therapy for moderate or severe AD—severe disease most appropriately managed initially with systemic therapy in a hospital setting (see Fig. 119-2).

FIGURE 119-2

Stepwise treatment for atopic dermatitis in adults and children. *(Reprinted, with permission, from Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I & part II. J Eur Acad Dermatol Venereol. 2018;32(5):657–682.)*



Reactive therapy is the traditional treatment modality where anti-inflammatory agents are used only during disease flares with moisturizers used alone between flare-ups. Proactive therapy includes a predefined, long-term, anti-inflammatory treatment applied intermittently (usually twice weekly) together with moisturizers and a predefined appointment schedule for clinical examinations which begins *after* all lesions have been successfully treated. The duration of proactive therapy is usually adapted to disease severity and persistence.[36]

Topical Corticosteroids

10 *Topical corticosteroids* (TCS) are the standard of care to which other treatments are compared.[10,11,30,36,38,42] They remain the drug treatment of choice for AD. However, despite their extensive use, supporting data are limited regarding optimal corticosteroid concentrations, duration and frequency of therapy, and quantity of application.[10,38] The use of long-term intermittent application of TCS was beneficial and safe in two randomized controlled trials (RCTs); however, independent studies of other formulations are needed.

To maximize the anti-inflammatory benefit and minimize adverse effects, the choice of TCS should be matched with the severity and site of disease. Low-potency TCS, such as hydrocortisone 1%, are suitable for the face, and medium-potency TCS, such as betamethasone valerate 0.1%, may be used

for the body. For longer-duration maintenance therapy, low-potency TCS are recommended.[38] Mid-strength and high-potency TCS should be used for short-term management of exacerbations.[38] There is no established optimum regimen for controlling flare-ups—starting with a short burst of high-potency TCS to rapidly control active disease followed by a rapid taper in potency is equally acceptable as using the lowest-potency agent thought to be needed then adjusting upward in potency if treatment fails.[38] Although twice-daily application is the usual clinical practice, there is some evidence of efficacy with once-daily use of some potent TCS.[38] Daily TCS applications are recommended until the inflammatory lesions are significantly improved—which may take up to several weeks at a time. Once control is achieved, either (a) stop the TCS and use moisturizers alone until the next flare-up, or (b) apply a TCS once or twice weekly to areas of the patient's body where frequent/repeated flare-ups occur—this method has reduced rates of relapse for those patients who experience frequent flare-ups at the same body sites[38] and should be used as proactive therapy in patients with moderate-to-severe AD.[36] There are different potencies for corticosteroids which should be used to guide therapy. (For a corticosteroid potency comparison chart, see Table 118-2 in Chapter 118, or visit the National Psoriasis Foundation Website at http://www.psoriasis.org/netcommunity/sublearn03_mild_potency.) Children should be treated with less-potent corticosteroids than adults.[36] Ultrahigh- and high-potency TCS, such as betamethasone dipropionate 0.05% or clobetasone propionate 0.05%, are typically reserved for short-term treatment of lichenified areas in adults.[41] After the lesions have cleared or significantly improved, a lower-potency agent (the least potent TCS that is effective)[38] should be used for maintenance when appropriate.[41] Potent fluorinated TCS should be avoided not only on the face, but also the genitalia and the intertriginous areas, and in young infants.[36]

It is also important to remember that altering the local environment through hydration and/or occlusion (eg, wet-wrap therapy)[11] as well as changing the vehicle[47] may alter the absorption and effectiveness of the TCS.[10] Some vehicles are better suited for certain body areas,[47] such as a lotion for the scalp and hairy areas. Foams may be more cosmetically pleasing to some patients, as they easily disappear into the skin. The surface area of the skin involved and the skin thickness also play a role. In addition, tachyphylaxis is a clinical concern, but there is little experimental documentation.

TCS are efficacious for the itch in addition to improving lesions, and itch is the key symptom for evaluation of response to treatment.[36] Tapering should not be initiated before the itch has largely improved.[36] Dose tapering has been suggested to avoid withdrawal rebound—with various tapering strategies such as to a less potent TCS or by reducing the frequency of application to intermittent treatment (eg, twice weekly).[36] Dose tapering also minimizes side effects.

Adverse effects of TCS may be systemic in nature, and they are directly related to the steroid potency, duration of use, and other factors as discussed above. Local adverse effects include striae distendae (stretch marks) and skin atrophy, perioral dermatitis, acne, rosacea, telangiectasias (rubeosis steroidica), purpura, focal hypertrichosis, a "dirty neck" (cutis punctata linearis colli), spontaneous scars (pseudocicatrices stellaires), and allergic contact dermatitis (often related to the vehicle but may be due to the corticosteroid).[36,38,48] Inappropriate, long-term use of potent TCS on the face can cause a facial rosacea-like disease with persistent erythema, burning and stinging sometimes called the "red face syndrome" or "corticosteroid addiction syndrome."[36] In infants, inappropriate use of high-potency TCS can cause granuloma gluteal infantum or iatrogenic Cushing's disease.[36] The potential for systemic adverse effects is related to the potency of the TCS, the site of application, the occlusiveness of the preparation, the percentage of body surface area covered, and the duration of use. Potential systemic side effects include hypothalamic-pituitary-adrenal (HPA) axis suppression, infections, hyperglycemia, cataracts, glaucoma, and growth retardation (in children).[1,36,38,46,48] However, growth retardation may also be related to the chronicity of the illness rather than to TCS use or dietary factors. Although less likely, systemic adverse effects can occur with low-potency TCS. For example, a phase II study of a mild-potency corticosteroid (desonide 0.05% foam) in children and adolescents 3 months to 17 years showed that 4% (3 out of 75) of patients experienced mild reversible HPA-axis suppression after a 4-week treatment period.[49]

When TCS therapy has failed for efficacy or safety reasons, numerous agents and interventions can be used as alternative or add-on therapy in patients with AD. Some of these interventions are steroid sparing.

Topical Calcineurin Inhibitors

11 Topical immunomodulators, such as the topical calcineurin inhibitors (TCIs): tacrolimus ointment (Protopic) and pimecrolimus cream (Elidel), have been shown to reduce the extent, severity, and symptoms of AD in adults and children.[10,36,38,41,42] TCIs inhibit the activation of key cells involved in AD, including T cells and mast cells, blocking the production of proinflammatory cytokines and mediators.[38] Tacrolimus also decreases the number

and costimulatory ability of epidermal DCs.[38] Pimecrolimus has more favorable lipophilic characteristics and, in animal studies, appears to preferentially distribute to the skin as opposed to the systemic circulation.[50] Both tacrolimus ointment and pimecrolimus cream are approved for AD in adults and children older than 2 years.[10,36,38,41,42] Although clinical trials conducted in younger infants (eg, 2-23 months old) showed significant efficacy without appreciable adverse effects, use in children younger than 2 years is not Food and Drug Administration (FDA)-approved.[51] Tacrolimus 0.03% ointment is approved for moderate-to-severe AD for children aged 2 years and older, with the 0.1% ointment limited to ages 16 years and older; pimecrolimus 1% cream is approved for mild-to-moderate AD for ages 2 years and older.[51] There is limited data comparing TCS with tacrolimus or pimecrolimus. However, it is known that simultaneous combination of TCS with TCI at the same site does not seem to provide greater benefit.[36] Using a TCI at sensitive skin sites such as face and skin folds while using TCS at other sites may be a useful strategy. Unlike TCS, long-term use of TCI does not cause skin atrophy[38]; however, an initial acute site reaction is fairly common.[36]

Proactive therapy (intermittent) using TCI is cost-effective for patients with moderate and severe AD.[36,52,53] However, cost-effectiveness of first-line treatment with TCI has not yet been conclusively demonstrated.[36]

The FDA has a black-box warning for both tacrolimus ointment and pimecrolimus cream about their potential cancer risk, but no causal relationship has been proven between use of a TCI and the development of lymphoma or nonmelanoma skin cancer in humans.[44] However, there is a theoretical potential of local skin carcinogenesis as discussed below. Thus, both tacrolimus and pimecrolimus are recommended for use as second-line treatments for short-term and noncontinuous chronic use in AD,[10,36,38,41,42] when the continued use of TCS is ineffective or inadvisable.[36,38] They may be appropriate in patients with corticosteroid-related adverse effects, patients with large body-surface areas of disease, patients unresponsive to TCS, or other reasons where treatment with TCS is inadvisable. Children and adults with a weakened or compromised immune system should not be treated with these agents.[38] Unlike TCS, TCI can be used on all body locations for prolonged periods,[36] although episodic use is recommended. They may be used as twice-weekly long-term therapy for maintenance.[11,36,52,53] They may be used as steroid-sparing agents (sequentially or concomitantly with TCS).[36,38]

The most common adverse effect of TCI is transient discomfort (burning sensation) at the application site.[36,38] Some patients may experience a transient worsening of skin conditions; and these transient side effects are more often seen with tacrolimus than pimecrolimus, and if applying to acutely inflamed skin.[36] Generalized viral infections (eg, eczema herpeticum, eczema molluscatum) have been reported.[36] There is a theoretical potential for local skin carcinogenesis as seen in animal studies, or for systemic effects if high blood levels are reached (eg, increased susceptibility to infections due to immunosuppressive effects).[51] Because of the theoretical possible risk of cutaneous malignancy in humans,[36,38] and the known long-term use of systemic cyclosporine being associated with increased photocarcinogenicity in solid organ transplant patients, sun protection is recommended.[11,36,46] However, it may be that the use of TCI has no association with increased risk of nonmelanoma skin cancer, other malignancies, or photocarcinogenicity.[54,55] Nonetheless, patients should be encouraged to apply a high sun protection factor (SPF) broad-spectrum sunblock daily to all exposed skin (ie, SPF 30 or higher); and this counseling should especially be emphasized for those patients with the highest risk of developing skin cancer, including patients with red hair and/or Fitzpatrick skin types I and II, and patients receiving phototherapy or using tanning beds.[46]

TCI are effective in relieving the associated pruritus. Both tacrolimus and pimecrolimus significantly relieve pruritus even after the first few days of treatment, in both children and adults (studies report relief after just 3 days).[10]

Coal Tar

Although tar preparations had been widely used for AD and have been recommended as alternative topical therapy, few RCTs support their efficacy.[38] Their anti-inflammatory properties are not well characterized, and part of the improvement may be the result of a placebo effect, which can be significant in AD.

Coal tar products are also staining and malodorous, although newer products may be more cosmetically acceptable. They are not recommended on acutely inflamed skin, since this may result in additional skin irritation.

The use of coal tar in pregnancy has not been studied. Few data are available about tar excretion into breast milk; in addition, safety in children has not been established.[56] Adverse effects include tar folliculitis, acneiform eruptions, irritant dermatitis, burning, stinging, photosensitivity, and a risk of tar

intoxication if used extensively in a young child.[56] Although animal studies showed that tar components can be converted to carcinogenic and mutagenic entities, there is inconclusive epidemiologic evidence supporting the claim that human use of topical tar preparations in dermatology leads to skin cancer.[56]

Selective Phosphodiesterase-4 Inhibitors

Crisaborole and apremilast are small-molecule phosphodiesterase (PDE)-4 inhibitors. Cyclic nucleotide PDEs break down cAMP and cGMP into inactive metabolites and there is increased PDE activity in AD, creating a proinflammatory state that may result in stimulation of Th_2 cells to release inflammatory mediators.[57,58] PDE-4 inhibitors inhibit the increased PDE activity; and crisaborole ointment is FDA-approved for treatment of mild-to-moderate AD in adults and children 2 years of age or older.[36] (Apremilast is approved for psoriasis and psoriatic arthritis [see Chapter 118, "Psoriasis," in this textbook].)[57] However, a pilot study of apremilast in patients with moderate-to-severe AD demonstrated moderate improvement of skin lesions, pruritus, and quality of life,[58] and it has also shown success for moderate-to-severe AD in children.[59]

Other Topical Therapies

Patients with moderate-to-severe AD who have frequent bacterial infections may benefit from dilute bleach baths with intranasal mupirocin—one study showed enhanced clinical improvement.[38] Janus kinase (JAK) inhibitors have shown evidence of efficacy for atopic dermatitis when administered either topically and orally. Topical JAK inhibitors include ruxolitinib and tofacitinib.[36]

Phototherapy

12 Phototherapy is effective for AD and is recommended[10,11,36,60] as second-line treatment when the disease is not controlled by TCS and/or TCI.[36,60] Although rarely used in prepubertal children, it is not contraindicated.[36] Both natural (heliotherapy) and artificial sources of UV radiation are effective.[36] UV light sources on the skin have immunosuppressive, immunomodulating, anti-inflammatory, and antipruritic effects.[36] A known mechanism of action is immunomodulation through apoptosis of inflammatory cells, inhibition of LCs, and alteration of cytokine production.[36] There are other potential benefits. Phototherapy may be steroid sparing, allowing for the use of lower-potency TCS, or even eliminating the need for maintenance by TCS in some cases. Phototherapy can be used for acute or maintenance therapy in children and adults with AD.[60] Phototherapy may also help prevent secondary bacterial skin infections, commonly seen in patients with AD. UVB radiation reduces *S. aureus* skin colonization.[36,61] However, in a few patients, phototherapy may worsen the AD; it is not recommended in patients whose disease flares up when exposed to sunlight. Relapse following cessation of therapy frequently occurs.[10]

Phototherapy may consist of either ultraviolet light therapy alone, or ultraviolet light therapy alongside drug or topical ointment (commonly called photochemotherapy). Psoralens plus ultraviolet A light (PUVA) is one type of photochemotherapy. The photosensitizer (psoralens) is administered either topically or in a bath immediately prior to ultraviolet A (UVA) light therapy. Topical ointments (such as crude coal tar) may also be used concomitantly with ultraviolet light therapy (eg, Crude coal tar + ultraviolet B [UVB] light) to increase efficacy.

Ultraviolet lamps include UVA (315-400 nm), UVA1 (340-400 nm), broadband UVB (BB-UVB) (280-315 nm), and narrowband UVB (NB-UVB) (311 nm). Phototherapies used for AD have included PUVA, high- or medium-dose UVA1, BB-UVB, and NB-UVB.[10,60] No definitive recommendation can be made to differentiate between the various phototherapies.[60] NB-UVB is more effective than BB-UVB therapy and is generally the most commonly recommended light treatment and it has a better side-effect profile than UVA or PUVA.[10,60] BB-UVB may not effectively treat the scalp and skinfold areas. Medium-dose UVA1 is effective for patients with an acute exacerbation of severe AD; however, the effect may be relatively short-lived and symptoms may recur within 3 months of stopping therapy.[60] Medium-dose UVA1 is considered similar in efficacy as NB-UVB; and high-dose UVA1 is preferred in severe cases when available.[10] There is weaker evidence supporting the use of PUVA in AD[47] and it is not first-choice.[10]

Patients need to wear eye protection during ultraviolet (UV) light therapy to prevent damage to the retina. Short-term adverse effects include erythema, skin pain, skin burning or sunburn, pruritus, and pigmentation.[60] Long-term adverse effects include premature aging of the skin (photoaging), lentigines, photosensitive eruptions, folliculitis, photo-onycholysis, HSV reactivation, facial hypertrichosis, and skin cancer.[60] For example, PUVA has

been associated with squamous cell carcinoma and possibly melanoma, which may occur years after PUVA therapy has ceased. UVA therapy may also cause cataract formation.[60]

To minimize a possible initial flare-up, co-medication of TCS and moisturizers has been suggested at the beginning of phototherapy.[36]

Other light therapies include short-wave visible light (>380 nm) ("blue light")—in uncontrolled pilot studies, photopheresis, and devices such as 308-nm monochromatic excimer lasers and pulsed-dye lasers—experimental.[36]

Systemic Therapies

Systemic therapies for the treatment of AD are generally not well studied. Small case series or open studies are available for some agents, but few well-conducted RCTs exist. Agents described in published papers have included systemic corticosteroids, cyclosporine, interferon-γ, azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIG), and biologic agents.[10,60] Systemic therapies are indicated in AD care only for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the disease, or where the quality of life is substantially affected.[60]

Systemic corticosteroids, although sometimes used for rapid disease suppression, are generally not recommended due to an unfavorable risk-benefit profile.[11,36,41,60] A 2017 systematic review of systemic treatment options for adults with AD gave no recommendations for use of systemic corticosteroids due to limited available evidence.[15] The 2018 European consensus guidelines recommended the following regarding oral corticosteroids for patients with AD: (1) restricted use, largely limited to adult patients; (2) short-term use (up to 1 week) in acute flare-ups only in exceptional cases; (3) daily dose not to exceed 0.5 mg/kg bodyweight; (4) use even more cautiously in children than in adults; (5) no long-term use.[36] Short courses of oral corticosteroids may lead to atopic flares/rebound.[11,60]

Cyclosporine is effective for AD and is considered the first-line treatment option when systemic therapy for AD is warranted, that is, for severe, recalcitrant AD,[10,11,15,36,60] but its usefulness is also limited by significant side effects, including hypertension and nephrotoxicity. Combination with UV therapy is not recommended, and effective UV protection should be used.[36] There is also the potential for significant drug-drug and drug-food (eg, grapefruit juice) interactions. It should be reserved for short-term use in adults (and more cautiously in children) with severe refractory disease.[11,60] Maximal benefit is usually seen after 2 to 6 weeks of use and relapse may occur quickly after cessation of therapy.[10,11,60] Treatment durations recommended are 6 to 9 months[11] and up to 1 year—this is off-label use in the United States and Canada.[60] European guidelines are for 2 years then to switch to another treatment if possible, but shorter intervals of 3 to 6 months are usually recommended; and cyclosporine is approved for AD in many European countries.[36] In a meta-analysis of eight RCTs, cyclosporine was more efficacious than placebo, with reduced body surface area, erythema, sleep loss, and glucocorticoid use. However, all scores were back to pretreatment levels 8 weeks after ending cyclosporine therapy.[10] An earlier study (2000) comparing intermittent to continuous cyclosporine therapy in children 12 to 16 years of age showed efficacy in some children on intermittent therapy (thus with a lower cumulative cyclosporine dose and minimizing toxicity); however, continuous cyclosporine therapy provided enhanced sustained improvement.[36,62]

Recombinant interferon-γ may be effective in a subset of patients with AD.[10] It may be an alternative for refractory AD (adults and children).[60] Two randomized placebo-controlled trials in patients with severe AD demonstrated significant improvement in symptoms.[63,64] Short-term adverse effects, such as headache, myalgias, and chills, occurred in substantial proportions of study patients. Transient liver transaminase elevations and granulocytopenia have also occurred. There is no recommended optimal dose.[60]

Azathioprine,[60,65] *methotrexate*,[60,66] *mycophenolate mofetil*,[60] and IVIG have shown efficacy in small case series or open-label studies primarily in adults with recalcitrant AD. There are two RCTs with azathioprine as monotherapy which showed efficacy, improving both QOL and AD.[60,65] Additional RCTs are needed. Oral methotrexate, with a long history of pediatric use for various inflammatory conditions, is effective in a case series of children (aged 2-16 years) with severe AD[66] and has also shown efficacy in adults.[60]

13 *Biologic agents* are beginning to be approved for AD in some countries. The safety and efficacy of various biologic agents in patients with AD have been studied, mostly in case reports, small case series, or open-label studies with a limited number of patients; however, larger randomized, placebo-

controlled trials are now available.[36] Tralokinumab is an IL-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in patients where topical therapies have proven ineffective. The recommended dose of tralokinumab is 600 mg subcutaneously once, followed by 300 mg subcutaneously every 2 weeks. It is supplied as 150 mg injections; thus, patients must administer multiple injections to receive the recommended dose. Common adverse effects of tralokinumab include injection site reactions, conjunctivitis, increased white blood cells, and upper respiratory tract infections. Patients on tralokinumab must not receive live vaccines because of an increased risk of infection.[35,36] Dupilumab, a fully human monoclonal antibody that blocks the common α-chain of the receptor for interleukin-4 and interleukin-13, was approved by the FDA in April 2017 for treating moderate-to-severe adult AD.[36] Dupilumab is a down-regulator of the JAK-STAT pathway. Clinical outcomes (SCORAD, EASI, IGA, BSA) as well as patient-reported outcomes (DLQI, pruritus rating scales) were improved in various phase I to III clinical trials in adults with AD.[67] Clinical trials in children are ongoing at the time of writing (NCT02407756) as well as open-label studies evaluating long-term safety and efficacy of repeat doses in children, adolescents, and adults with previous participation in dupilumab clinical trials (NCT02612454, NCT01949311).[15] Dupilumab's safety profile is superior to conventional immunosuppressives such as cyclosporine or methotrexate; its most relevant side effects being conjunctivitis and injection site reactions.[67] Safety in pregnancy is unknown at the time of writing. A recent review of systemic treatment options for adults with AD discussed trials with other biologics including infliximab, mepolizumab, omalizumab, rituximab, and ustekinumab.[15] Some of these trials showed little to no improvement; however, a case series of ustekinumab use showed promising results and was well tolerated.[15] Nemolizumab is another biologic with some promise in a recent clinical trial especially in reducing pruritus.[36] The TNF-α inhibitors infliximab and etanercept is effective in a few patients but not others, and adverse events have included infusion reactions with flushing and dyspnea, urticaria, and recurrent skin infections of methicillin-resistant *S. aureus*. Similarly, omalizumab, rituximab, and alefacept have been shown in a few case reports and small case series to be somewhat effective. A case report series of omalizumab plus IVIG showed significant clinical improvement.[68] However, an RCT with omalizumab showed no clinical improvement in AD despite reducing IgE levels.[60] Therapy of AD with traditional biologics (eg, rituximab, omalizumab, or ustekinumab) is not recommended.[36]

Upadacitinib and abrocitinib are oral selective JAK-1 inhibitors approved by the FDA for treatment of moderate-to-severe atopic dermatitis. Upadacitinib was compared to dupilumab in a 24-week, head-to-head, phase 3b multicenter RCT in adults with moderate-to-severe AD with results showing superior efficacy of upadacitinib vs dupilumab in Eczema Area and Severity Index (EASI75) ($p = 0.006$) and all secondary endpoints such as worst pruritis NRS.[69] There were other clinical trials with upadacitinib involving adults and children older than 12 years, and it has received FDA approval for use at 15 and 30 mg once daily as monotherapy for those age groups. Abrocitinib has received FDA approval based on the results of five clinical trials for use in adults only, at 100 and 200 mg doses, with the 200 mg dose reserved for patients unresponsive to the 100 mg dose. Both products carry a warning of increased risk of serious infections, mortality, malignancy, major adverse cardiovascular events, and thrombosis.

Alitretinoin is a retinoid with anti-inflammatory and antiproliferative effects licensed in some European countries for treatment of hand eczema.[36] It may improve both extrapalmar and hand lesions in AD patients and may be used for atopic hand eczema in adult patients of non-childbearing potential unresponsive to TCS therapy.[36]

Oral antihistamines are used widely; however, there is mixed evidence of efficacy in AD control.[36,60] There is some evidence that oral sedating antihistamines used at night may benefit patients with AD with poor sleep due to pruritus.[11,60]

Complementary and Alternative Therapies

Traditional Chinese herbal therapy has been studied in placebo-controlled trials and provide temporary benefit for patients with severe AD. However, the effectiveness may wear off despite continued treatment, and long-term toxicity is unknown.[10,70] A recent meta-analysis of seven RCTs attempted to evaluate the efficacy and safety of oral Chinese medicines for AD and concluded that traditional Chinese herbal medicines significantly improved symptom severity and was well tolerated; however, the studies were of poor quality and did not allow for valid conclusions to be drawn about tolerability and routine use.[71] Additional studies are needed.

Probiotics and *prebiotics* may prove to be beneficial for prevention and treatment of AD. Probiotics are live microorganisms (bacteria or fungi) that confer a health benefit on the host when administered in adequate amounts.[72] Prebiotics are nondigestable compounds that lead to favorable changes in the gut microbiome.[72] The term "synbiotics" refers to products that contain both probiotics and prebiotics.[72]

Although earlier studies of *probiotics* had mixed results, more recent clinical trials showed evidence of benefit in both prevention and treatment of AD.[72-75] The most common species of probiotics used include *Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus johnsonii, Bifidobacterium lactis*, and *Saccaromues boulardii*.[72] A meta-analysis of 25 clinical trials concluded that probiotics significantly reduced the risk of atopic sensitization when given prenatally.[72,73] A double-blind RCT showed that probiotics reduced the SCORAD index and serum cytokines in AD patients.[72,74] A randomized trial of oral *Bifidobacterium bifidum* in 40 infants newly diagnosed with AD noted a significant reduction in the SCORAD index posttreatment in the infants receiving the probiotic versus no change in those who did not.[75]

Prebiotics are nondigestible oligosaccharides including fructooligosaccharides, galactooligosaccharides, lactulose, and inulin. These can stimulate the growth of selective beneficial gut bacteria, in particular lactobacilli and bifidobacteria.[72] In the colon, prebiotics are fermented into short chain fatty acids (SCFAs) including butyrate, acetate, and propionate. The SCFAs may alter the gut microbiome. For example, transgalactooligosaccharides increase the number of bifidobacteria and modify the colonic fermentation metabolism of the gut flora.[76] Prebiotics have shown benefits for various disease conditions including hypercholesterolemia, *Clostridium difficile*–associated diarrhea, and allergic conditions such as AD.[72] Two recent meta-analyses have shown a 32% reduced incidence of pediatric AD[77] and that the combination of galactooligosaccharide and fructooligosaccharide reduced AD incidence.[78]

Immunotherapy using allergen-specific desensitization techniques in controlled settings for patients with AD may also be beneficial, and much research is ongoing including RCTs. A recent review and meta-analysis of immunotherapy in patients with AD showed significant efficacy.[11,79] More research is also needed to adequately assess the role of homeopathy, hypnotherapy, acupuncture, massage therapy, and biofeedback therapy in the treatment of AD.

Patient Considerations

14 AD may have significant implications not only for the patients themselves, but also their families and caregivers. The burden of AD needs to be addressed. There is strong evidence that AD in adults is associated with select allergic, atopic, immune-mediated, mental health, and bone health comorbidities and skin infections.[37] In addition, patients with refractory AD may need further follow-up to rule out other diagnoses, confirm adequate/appropriate first-line therapy use, rule out/minimize exacerbating factors, and implement second-line therapies.[80]

In 2006, an international study of 2,002 patients and caregivers from eight countries addressed the effect of AD on the lives of patients and society.[81] This European study found that, on average, patients experienced nine flares per year, with those having severe disease experiencing more flares and taking significantly longer to clear. The flares were associated with disturbed sleep, and 86% of patients avoided at least one type of everyday activity. Schoolwork performance and productivity were negatively affected. Patients missed an average of 2.5 days of school or work per year, and an analysis of adult patient performance at work and occupational absence showed that the social cost of lost productivity could amount to more than 2 billion Euros per year across the European Union. There were also emotional consequences; half of the patients experienced depression or unhappiness about their condition, and one-third reported that AD had eroded their self-confidence. In addition, concern about adverse effects from TCS treatments resulted in poor adherence to therapy. On average, patients endured the symptoms of AD without initiating specific treatment 47% of the time they had an exacerbation. Approximately one-half of the respondents were concerned about using TCS, and 58% restricted them to particular sites, 39% used them less frequently or for shorter time periods than prescribed, and 66% used them as a last resort. The study concluded that AD is "an undertreated disease that has a significant, yet mostly avoidable, negative effect on patients, their caregivers, and society."[81]

The above conclusion is echoed in more recent reports. In 2018 and 2019, studies relating to the burden of disease from the United States, Canada, and internationally were published. In a 2018 US cross-sectional study, 1,519 adult patients with AD reported a multidimensional burden of disease that is higher with greater disease severity and inadequate disease control.[82] Patients with moderate/severe AD (830/1519) reported more severe itching and pain, greater adverse effects on sleep, higher prevalence of anxiety and depression, and greater health-related QoL impairment. About 103/1,519 patients had inadequate disease control despite treatment with systemic immunomodulators or phototherapy, and they reported higher burdens of itch and sleeping symptoms versus those with controlled disease.[82] Sleep symptoms included trouble sleeping (significant on PO-SCORAD), longer sleep latency, more frequent sleep disturbances, and greater need for OTC sleep medications.[82] Results from two 2018 Canadian online national cross-sectional surveys included the burden of moderate-to-severe AD on pediatric patients.[83] For the adult patients: 87% (187/216)

reported that their daily life was negatively affected by their disease, with experiences ranging from dysfunctional sleep (79%, ie, 148/187), anxiety (64%, ie, 120/187), avoidance of social activities (48%, ie, 90/187), avoidance of physical activity (47%, ie, 88/187), and avoidance of intimacy (40%, ie, 75/187). In addition, 32% reported difficulty accessing treatments and 41% felt that their treatment needs were unmet. Only 9% reported that their disease was well controlled, and 78% reported they had lived for over 1 year with inadequate treatment for their disease. For the pediatric patients: 78% (253/361) had sleep disturbances, 51% avoided social activities, 30% had anxiety issues, 20% missed school due to their AD—and of these, 23% have missed 10 days or more within the past year.[83] Regardless of treatment modalities, most survey respondents felt that their child's AD is not well controlled—85% have used three or more treatment modalities for their child's AD, and 80% of respondents find the recommended care regimen for their child's AD challenging.[83]

In 2019, data from a 2016 National Health and Wellness Survey conducted in France, Germany, Italy, Spain, and the United Kingdom was published with comparisons between controls without AD matched to patients with self-reported AD (both $n = 1,860$).[84] Self-reported comorbidities were significantly more prevalent in patients with AD compared to those without AD and these included anxiety, depression, and sleep disturbances. There was reduced health-related QoL as well as a significant impact on work productivity (ie, presenteeism and overall work impairment) and the ability to undertake activities. There was also greater healthcare utilization.[84]

Even though there is likely selection bias due to the self-reporting nature of these surveys, the results from these (and others) should alert healthcare professionals to the continuing unmet health, psychosocial, and educational needs associated with AD.

Patient communication may be a key step—treating them as partners in their own (or their child's) care, with regular contact, advice, and support. Healthcare professionals play an integral role in providing patient and caregiver education and support about this disease and specific treatment plans. The importance of adequate and appropriate education for the patient, family, and caregivers about AD and its management cannot be overemphasized. Patients should be involved in their own care whenever possible. Timely access to dermatology consultation may be another key factor—in the above Canadian survey only 27% (123/451) of respondents are managed by a dermatologist—wait times for appointments were 3 months or longer (46%) and in 25% of cases were 6 months or longer.[81] Limited access to care is a societal issue.

EVALUATION OF THERAPEUTIC OUTCOMES

- Contact patient/caregiver in 1 to 2 weeks to follow-up about the efficacy of recommended therapies and any issues with the treatment regimen. Continuing regular follow-up is recommended to monitor for adherence and address other issues and patient concerns (eg, QoL issues as discussed above).
- Ensure that appropriate monitoring parameters for efficacy and potential adverse effects have been put in place (eg, follow-up lab tests as needed).
- Reinforce preventive measures including continuation of proactive therapy, if implemented.
- Ensure that patient/caregiver has been connected to other health resources as needed for follow-up (eg, a dermatologist, psychologist, and social worker).

CONCLUSION

AD is a chronic skin condition that generally presents at an early age. It affects the patient, family, caregivers, and our society and is optimally managed by multidisciplinary care. Nonpharmacologic management strategies are important in treatment; these include appropriate skin care, hydration, avoidance of triggers, and psychosocial support and management. Community pharmacists are in a prime position to support patients, physicians, and other health professionals because patients with AD (and caregivers of children with AD) may initially seek nonprescription treatments.[30] The pharmacologic treatment strategy may be proactive or reactive depending on disease severity. Treatment alternatives continue to emphasize TCS as the standard of care; others being TCIs and other topical agents, wet wrap therapy, and UV therapy. For severe/recalcitrant disease, systemic therapies including cyclosporine and biologics may be warranted. A 2018 review provides a step-wise clinical approach to the patient with refractory AD which include ruling out other diagnoses, confirming first-line therapies, and ruling out exacerbating factors before using second-line therapies; further, a multidisciplinary approach to address behavioral factors (poor adherence, improper technique, habitual scratching, depression, sleep disturbance,

stress) is described (eg, habit reversal training for the itch-scratch cycle).[80] Patient and caregiver education and support about AD and treatment strategies is critical to optimize treatment outcomes. Successful outcomes result when patients and caregivers are partners with healthcare professionals in the management of this chronic disease.

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ABBREVIATIONS

AD	atopic dermatitis
AMP	antimicrobial peptide
BB-UVB	broadband ultraviolet B light (280-315 nm)
DC	dendritic cell
ETFAD	European Task Force of Atopic Dermatitis
FDA	Food and Drug Administration
FLG	filaggrin gene
GI	gastrointestinal
HPA	hypothalamic-pituitary-adrenal
IgE	immunoglobulin E
IgM	immunoglobulin M
IL	interleukin
ISAAC	International Study of Asthma and Allergies in Childhood
IVIG	intravenous immunoglobulin
JAK	Janus kinase
MDC	macrophage-derive chemoattractant
NB-UVB	narrowband ultraviolet B light (311 nm)
NIAID	National Institute of Allergy and Infectious Diseases
PDE	phosphodiesterase
PUVA	psoralens plus ultraviolet A light

RAST	radioallergosorbent test
RCT	randomized controlled trial
SCFAs	short-chain fatty acids
SCORAD	Scoring of Atopic Dermatitis
SD	standard deviation
SPF	sun protection factor
TARC	thymus and activation-regulated chemokine
TCIs	topical calcineurin inhibitors
TCS	topical corticosteroids
TH_1	T-helper cell type 1
TH_2	T-helper cell type 2
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B

REFERENCES

1. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Atopic Dermatitis. US Department of Health and Human Services. 2018. Available at: https://www.niams.nih.gov/health-topics/atopic-dermatitis. Accessed February 5, 2022.

2. Eichenfield LE, Tom WL, Chamlin SI, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014;70:338–351. [PubMed: 24290431]

3. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016 (March 12);387(10023):1109–1122. [PubMed: 26377142]

4. Hanifin JM. Epidemiology of atopic dermatitis. *Immunol Allergy Clin North Am.* 2002;22:1–24.

5. Bieber T. Mechanisms of disease: Atopic dermatitis. *N Engl J Med.* 2008;358:1483–494. [PubMed: 18385500]

6. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol.* 2006;118:209–213. [PubMed: 16815157]

7. Williams H, Stewart A, von Mutius E, Cookson W, et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol.* 2008;121:947–954. [PubMed: 18155278]

8. DaVeiga SP. Epidemiology of atopic dermatitis: A review. *Allergy Asthma Proc.* 2012;23:227–234.

9. Nutten S. Atopic dermatitis: Global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66(suppl 1):8–16. [PubMed: 25925336]

10. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I & part II. *J Eur Acad Dermatol Venereol.* 2018;32(5):657–682. [PubMed: 29676534]

11. Plotz SG, Wiesender M, Todorova A, Ring J. What is new in atopic dermatitis/eczema? *Expert Opin Emerging Drugs*. 2014;19(4):441–458.

12. Akdis CA. New insights into mechanisms of immunoregulation in 2007. *J Allergy Clin Immunol.* 2008;122:700–709. [PubMed: 19014761]

13. Ege MJ, Herzum I, Buchele G, et al. Prenatal exposure to a farm environment modifies atopic sensitization at birth. *J Allergy Clin Immunol.* 2008;122:407–412. [PubMed: 18678343]

14. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. *Curr Probl Dermatol.* 2011;41:1–34. [PubMed: 21576944]

15. Gooderham M, Lynde CW, Papp K, et al. Review of systemic treatment options for adult atopic dermatitis. *J Cutan Med Surg.* 2017;21(1):31–39. [PubMed: 27635033]

16. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Eng J Med.* 2011;365(4):1315–1327.

17. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust rick factors in atopic disease. *J Allergy Clin Immunol.* 2009;123:1361–1370. [PubMed: 19501237]

18. Honey B, Steinhoff M, Ruzicka T, Leung DYM. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol.* 2006;118:178–189. [PubMed: 16815153]

19. Leung DYM. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. *J Allergy Clin Immunol.* 2009;124:494–495. [PubMed: 19733296]

20. Steinke JW, Rich SS, Borish L. Genetics of allergic disease. *J Allergy Clin Immunol.* 2008;121(suppl):S384–S387. [PubMed: 18241687]

21. Heratizadeh A, Wichmann K, Werfel T. Food allergy and atopic dermatitis: How are they connected? *Curr Allergy Asthma Rep.* 2011;11:284–291. [PubMed: 21614611]

22. Sicherer SC, Leung DYM. Advances in allergic skin disease, anaphylaxis and hypersensitivity reactions to foods, drugs, and insects in 2008. *J Allergy Clin Immunol.* 2009;123:319–327. [PubMed: 19203656]

23. Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol.* 2008;122:261–266. [PubMed: 18439663]

24. Novak N, Bieber T. Dendritic cells as regulators of immunity and tolerance. *J Allergy Clin Immunol.* 2008;121(suppl):S370–S374. [PubMed: 18241684]

25. Biebe T, de la Salle H, Wollenberg A, et al. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *J Exp Med.* 1992;175:1285–1290. [PubMed: 1533242]

26. Wang B, Rieger A, Kilgus O, et al. Epidermal Langerhans cells from normal human skin bind monomeric IgE via Fc epsilon RI. *J Exp Med.* 1992;175:1353–1365. [PubMed: 1533243]

27. Novak N, Bieber T. The role of dendritic cell subtypes in the pathophysiology of atopic dermatitis. *J Am Acad Dermatol.* 2005;53(suppl 2):S171–S176. [PubMed: 16021172]

28. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol.* 2008;121:1331–1336. [PubMed: 18539191]

29. Boyce JA, Assa'ad AH, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States. Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010;126(6 suppl):S1–S58. Available at: https://www.niaid.nih.gov/diseases-conditions/food-allergy. Accessed February 5, 2022. [PubMed: 21134576]

30. Wong ITY, Tsuyuki RT, Cresswell-Melville A, et al. Guidelines for the management of atopic dermatitis (eczema) for pharmacists. *Can Pharm J.* 2017;150(5):285–297.

31. Lucas JSA, Lewis SA, Jourihane JO'B. Kiwi fruit allergy: A review. *Pediatr Allergy Immunol.* 2003;14:420–428. [PubMed: 14675467]

32. Cohen A, Goldberg M, Levy B, et al. Sesame food allergy and sensitization in children: The natural history and long-term follow-up. *Pediatr Allergy Immunol.* 2007;18:217–223. [PubMed: 17346302]

33. Burks AW, Laubach S, Jones SM. Oral tolerance, food allergy, and immunotherapy: Implications for future treatment. *J Allergy Clin Immunol.* 2008;121:1344–1350. [PubMed: 18410959]

34. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis. Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol.* December 2014;71(6):1218–1233. 10.1016/j.jaad.2014.08.038.

35. Kim BS. Atopic Dermatitis. Medscape eMedicine updated Feb 13, 2023. Available at: http://emedicine.medscape.com/article/1049085-overview. Accessed September 13, 2023.

36. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I. *J Eur Acad Dermatol Venereol.* 2018;32:657–682. [PubMed: 29676534]

37. Davis Dawn MR, Drucker Aaron M, Alikhan Ali, et al. AAD Guidelines: Awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol.* 2022. 10.1016/j.jaad.2022.01.009.

38. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71:116–132. [PubMed: 24813302]

39. Angelova-Fischer I, Neufang G, Jung K, et al. A randomized, investigator-blinded efficacy assessment study of stand-alone emollient use in mild to moderately severe atopic dermatitis flares. *J Eur Acad Dermatol Venereol.* 2014;(suppl 3):9–15.

40. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol.* 2014;134:824–830. e6. [PubMed: 25282564]

41. Rubel D, Thirumoorthy T, Soebaryo W, et al. Consensus guidelines for the management of atopic dermatitis: An Asia-Pacific perspective. *J Dermatol.* 2013;40:160–171. [PubMed: 23289827]

42. Baron SE, Cohen SN, Archer CB. British Association of Dermatologists and Royal College of General Practitioners. Guidance on the diagnosis and clinical management of atopic eczema. *Clin Exp Dermatol.* 2012;37(suppl 1):7–12. [PubMed: 22486763]

43. Aries MF, Hernandez-Pigeon H, Vaissiere C, et al. Anti-inflammatory and immunomodulatory effects of *Aquaphilus dolomiae* extract on in vitro models. *Clin Cosmet Investig Dermatol.* 2016;9:421–434. [PubMed: 27877060]

44. Bianchi P, Theunis J, Casas C, et al. Effects of a new emollient-based treatment on skin microflora balance and barrier function in children with mild atopic dermatitis. *Pediatr Dermatol.* 2016;33:175–171.

45. Fostini AC, Georgescu V, Decoster CI, Girolomini G. A cream based on *Aquaphilus dolomiae* extracts alleviates non-histaminergic pruritus in

humans. *Eur J Dermatol.* 2017;27:317–318. [PubMed: 28414196]

46. Law RM, Kwa PG, Maibach HI, et al. Atopic dermatitis: The itch that erupts when scratched. In: Schwinghammer TL, ed., et al. *Pharmacotherapy Casebook: A Patient-Focused Approach*. 11th ed. New York: McGraw-Hill; 2020.

47. Rosso JD, Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. *J Am Acad Dermatol.* 2005;53:S50–S58. [PubMed: 15968264]

48. Hengge UR, Ruzicka T, Schwartz RA, et al. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol.* 2006;54:1–15. [PubMed: 16384751]

49. Hebert AA; Desonide Foam Phase III Clinical Study Group. Desonide foam 0.05%: Safety in children as young as 3 months. *J Am Acad Dermatol.* 2008;59:334–340. [PubMed: 18638631]

50. Stuetz A, Grassberger M, Meingassner JG. Pimecrolimus (Elidel, SDZ ASM 981)—Preclinical pharmacologic profile and skin selectivity. *Semin Cutan Med Surg.* 2001;20:233–241.

51. Berger TG, Duvic M, Van Voorhees AS, Frieden IJ. The use of topical calcineurin inhibitors in dermatology: Safety concerns. *J Am Acad Dermatol.* 2006;54:818–823. [PubMed: 16635663]

52. Healy E, Bentley A, Fidler C, Chambers C. Cost-effectiveness of tacrolimus ointment in adults and children with moderate and severe atopic dermatitis: Twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective. *Br J Dermatol.* 2011;164:387–395. [PubMed: 21083544]

53. Thaci D, Chambers C, Sidu M, et al. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: Clinical efficacy and economic impact over 12 months. *J Eur Acad Dermatol Venereol.* 2010;24:1040–1046. [PubMed: 20158589]

54. Margolis DJ, Abuabara K, Hoffstad OJ, et al. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol.* 2015;151:594–599. [PubMed: 25692459]

55. Deleuran M, Vewtergaard C, Volund A, et al. Topical calcineurin inhibitors, topical glucocorticoids and cancer in children: A nationwide study. *Acta Derm Venereol.* 2016;96:834–835. [PubMed: 26934868]

56. Pughdal KV, Schwartz RA. Topical tar: Back to the future. *J Am Acad Dermatol.* 2009;61:294–302. [PubMed: 19185953]

57. Kitzen JM, Pergolizzi JV, Taylor R, et al. Crisaborole and apremilast: PDE4 inhibitors with similar mechanism of action, different indications for management of inflammatory skin conditions. *Pharmacology & Pharmacy*. 2018;9:357–381.

58. Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Arch Dermatol.* 2012;148:890–1108. [PubMed: 22508772]

59. Saporito RC, Cohen DJ. Apremilast use for moderate-to-severe atopic dermatitis in pediatric patients. *Case Rep Dermatol.* 2016;8:179–184. [PubMed: 27504087]

60. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014;71:327–349. [PubMed: 24813298]

61. Dotterud LK, Wilsgaard T, Vorland LH, et al. The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and health controls. *Int J Circumpolar Health*. 2008;67:254–260. [PubMed: 18767345]

62. Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: Short course versus continuous therapy. *Br J Dermatol.* 2000;142:52–58. [PubMed: 10651694]

63. Hanifin JM, Schneider LC, Leung DY, et al. Recombinant interferon gamma therapy for atopic dermatitis. *J Am Acad Dermatol.* 1993;28:189–197. [PubMed: 8432915]

64. Jang IG, Yang JK, Lee HJ, et al. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *J Am Acad Dermatol.* 2000;42:1033–1040. [PubMed: 10827410]

65. Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine doses by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: A double-blind, randomized controlled trial. *Lancet*. 2006;367:839–846. [PubMed: 16530578]

66. Rouse C, Siegfried E. Methotrexate for atopic dermatitis in children. *J Am Acad Dermatol.* 2008;58(2 suppl 2):AB7, abstract P608.

67. Seegraber M, Srour J, Walter A, et al. Dupilumab for treatment of atopic dermatitis. *Expert Rev Clin Pharmacol.* 2018;11(5):467–474. [PubMed: 29557246]

68. Toledo F, Silvestre JF, Munoz C. Combined therapy with low-dose omalizumab and intravenous immunoglobulin for severe atopic dermatitis. Report of four cases. *J Eur Acad Dermatol Venereol.* 2012;26:1325–1327. [PubMed: 22050044]

69. Blauvelt Andrew, Teixeira Henrique D, Simpson Eric L, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis. *JAMA Dermatology*. 2021;157:1047–1055. 10.1001/jamadermatol.2021.3023.

70. Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. *Arch Dermatol.* 1998;134:1388–1393. [PubMed: 9828872]

71. Tan HY, Zhang AL, Chen DC, et al. Chinese herbal medicine for atopic dermatitis: A systematic review. *J Am Acad Dermatol.* 2013;69:295–230. [PubMed: 23759835]

72. Patel R, DuPont HL. New approaches for bacteriotherapy: Prebiotics, new-generation probiotics, and synbiotics. *Clin Infect Dis.* 2015;60(suppl 2):S108–S121. [PubMed: 25922396]

73. Elazab N, Mendy A, Gasana J, et al. Probiotic administration in early life, atopy, and asthma: A meta-analysis of clinical trials. *Pediatrics*. 2013;132:e666–e676. [PubMed: 23958764]

74. Yesilova Y, Calka O, Akdeniz N, et al. Effect of probiotic on the treatment of children with atopic dermatitis. *Ann Dermatol.* 2012;24:189–193. [PubMed: 22577270]

75. Lin RJ, Qiu LH, Guan RZ, et al. Protective effect of probiotics in the treatment of infantile eczema. *Experimental and Therapeutic Medicine*. 2015;9:1593–1596. [PubMed: 26136864]

76. Bouhnik Y, Flourie B, D'Agay-Abensour L, et al. Administration of transgalato-oligosaccharides increases fecal bifidobacteria and modifies colonic fermentation metabolism in healthy humans. *J Nutr.* 1997;127:444–448. [PubMed: 9082028]

77. Baquerizo Nole KL, Yim E, Keri JE. Probiotics and prebiotics in dermatology. *J Am Acad Dermatol.* 2014;71:814–821. [PubMed: 24906613]

78. Osborn DA, Sinn J. Prebiotics in infants for prevention of allergy. *Cochrane Database Syst Rev.* 2013;3.

79. Bae JM, Choi YY, Park CO, et al. Efficacy of allergen-specific immunotherapy for atopic dermatitis: A systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol.* 2013;132:110–117. [PubMed: 23647790]

80. Izadi N, Leung DYM. Clinical approach to the patient with refractory atopic dermatitis. *Ann Allergy Asthma Immunol.* 2018;120(1):23–33.e1. doi: 10.1016/j.anai.2017.09.061.

81. Zuberbier T, Orlow SJ, Paller AS, et al. Patient perspectives on the management of atopic dermatitis. *J Allergy Clin Immunol.* 2006;118:226–232. [PubMed: 16815160]

82. Simpson EL, Guttman-Yassky E, Margolis DJ, et al. Association of inadequately controlled disease and disease severity with patient-reported disease burden in adults with atopic dermatitis. *JAMA Dermatol.* 2018;154(8):903–912. doi: 10.1001/jamadermatol.2018.1572.

83. Bridgman AC, Eshtiaghi P, Cresswell-Melville A, Ramien M, Drucker AM. The burden of moderate to severe atopic dermatitis in Canadian children: A cross-sectional survey. *J Cutan Med Surg.* 2018;22(4):443–444. doi: 10.1177/1203475418761859.

84. Eckert L, Gupta S, Gadkari A, Mahajan P, Gelfand JM. Burden of illness in adults with atopic dermatitis: Analysis of National Health and Wellness Survey data from France, Germany, Italy, Spain, and the United Kingdom. *J Am Acad Dermatol.* 2019;81(1):187–195. doi: 10.1016/j.jaad.2019.03.037.

SELF-ASSESSMENT QUESTIONS

1. Baby JS is a 7-month-old infant who has been diagnosed with atopic dermatitis. Clinical signs and symptoms she presented with may include all the following EXCEPT:

   A. Pruritus

   B. Hypopigmentation

   C. Facial eruptions

   D. Secondary bacterial infection

2. Appropriate nonpharmacologic therapy for Baby JS (7 months of age) includes all of the following EXCEPT:

   A. Moisturizer applied *ad lib*

   B. Bathing five times a day

   C. Keep humidity at or above 50%

   D. Keep June cool—avoid situations of overheating

3. Initial pharmacologic therapy for Baby JS (7 months of age) should be:

   A. Topical corticosteroid

   B. Topical pimecrolimus

   C. Oral prednisone

   D. Phototherapy with UVB

4. The defect thought to play a key role in atopic dermatitis is:

   A. Mutations of the filaggrin gene

   B. Absence of the epidermal growth hormone

   C. Presence of the Philadelphia chromosome

   D. Abnormal CFTR protein

5. An immune system change associated with atopic dermatitis is:

   A. Reduced serum IgE

   B. Increased interleukin-12

   C. Increased Th_2 cell activity

   D. Increased blood neutrophils

6. Miss SB is a 15-year-old girl with atopic dermatitis who has multiple food allergies. The most allergenic foods that Susanne might be allergic to would include all of the following EXCEPT:

   A. Eggs

   B. Milk

   C. Bananas

   D. Strawberries

7. Miss SB (15-year-old girl with atopic dermatitis) was assessed for disease severity by her dermatologist—who used the SCORAD. She has significant pruritus and her sleep was generally restless with multiple wakenings during the night. Her SCORAD score was 40. This means that Susanne's atopic dermatitis is:

   A. Mild

   B. Moderate

   C. Severe

   D. Very severe

8. Miss SB (15-year-old girl with atopic dermatitis) also has yellow crusting lesions on her skin which was diagnosed as a bacterial infection. The most likely organism is:

   A. *Staphylococcus aureus*

   B. *Pseudomonas aeruginosa*

   C. *Streptococcus viridians*

   D. *Xenotrophomonas maltophilia*

9. Miss SB (15-year-old girl with atopic dermatitis) has required pimecrolimus 1% cream during her flare-ups. Appropriate counseling for SB would include:

   A. Apply the cream only on lichenified areas

   B. Use the cream three to four times a day

   C. It is very uncommon for the cream to cause a burning sensation

   D. Wear a sunscreen with SPF 30 or higher

10. Which of the following treatment alternative would be preferred in a pregnant patient with atopic dermatitis?

    A. Topical corticosteroid

B. Oral cyclosporine

C. Injectable dupilumab

D. Phototherapy with PUVA

11. The most effective type of phototherapy for atopic dermatitis is:

A. Broadband UVB

B. Narrowband UVB

C. PUVA

D. Low-dose UVA

12. Potential concerns with biologic agents (eg, dupilumab) include all of the following EXCEPT:

A. Allergic reactions

B. Infections

C. Carcinogenesis

D. Skin atrophy

13. Potential concerns with oral cyclosporine include all of the following EXCEPT:

A. Hypertension

B. Nephrotoxicity

C. Hepatotoxicity

D. Interaction with grapefruit juice

14. Ultrahigh- and high-potency topical corticosteroids include all of the following EXCEPT:

A. Betamethasone valerate

B. Betamethasone dipropionate

C. Clobetasone propionate

D. Diflorasone diacetate

15. Appropriate use of oral prednisone for atopic dermatitis include all of the following EXCEPT:

A. For severe, recalcitrant, chronic atopic dermatitis

B. For rapid relief of severe refractory disease while transitioning to other therapies

C. Discontinue abruptly after a short 5-day course

D. Provide intensified skin care with topical corticosteroids and moisturizers

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Hypopigmentation is not a feature of AD, the others are.
2. **B.** Bathing should usually not be more often than once (to twice) a day.
3. **A.** Topical corticosteroids remain the treatment of choice for AD. Calcineurin inhibitors such as pimecrolimus are second-line, but in this case of a 7-month-old they would not be recommended.
4. **A.** FLG mutations remain the most significant defect in AD.
5. **C.** Increased TH_2 activity is a significant pathophysiologic change in AD.
6. **C.** The other foods are more often associated with AD/seen in patients with food allergies.
7. **B.** A SCORAD score between 25 and 50 is considered moderate disease.
8. **A.** *Staphylococcus epidermidis* (coagulative negative Staph) is a skin commensal and most likely to be the causative agent.
9. **D.** This relates to the potential concern of skin carcinogenesis and possibly increased risk with sun exposure. Thus, sunscreen use (SPF >30) is recommended.
10. **A.** Topical corticosteroid is first-line therapy for AD including in pregnancy. The others are systemic therapies or have a systemic component (PUVA), thus greater risk to the baby. Corticosteroids are safe to use in pregnancy.
11. **B.** NB-UVB is the most effective and least toxic.
12. **D.** The other options are potential side effects/toxicity of biologic agents.
13. **C.** Oral cyclosporine may be nephrotoxic but not hepatotoxic.
14. **A.** Betamethasone *valerate* is a midpotency corticosteroid. Note that the salt makes a difference to corticosteroid potency.
15. **C.** Abrupt disruption may result in a disease flare.