Atopic Dermatitis

A Common Pediatric Condition and Its Evolution in Adulthood

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KEYWORDS

• Atopic dermatitis • Eczema • Pruritus • Atopy • Corticosteroids • Phototherapy • Bleach bath

KEY POINTS

- Clinical presentation of atopic dermatitis varies from infancy to adulthood, and it is important for the clinician to recognize these different presentations.
- Atopic dermatitis has a significant effect on an individual's quality of life.
- Atopic dermatitis is associated with multiple comorbidities.
- Treatment of atopic dermatitis is multifactorial and targeted at the various components of pathogenesis.
- The treatment and management of atopic dermatitis is similar across age groups.

PATIENT HISTORY/SYMPTOMS

Atopic dermatitis (AD), which is also more commonly referred to as eczema, is a common chronic and pruritic inflammatory skin disorder with a relapsing course that can affect any age group.[1] The term *atopic* or *atopy* refers to a tendency to develop an increased sensitivity to common environmental antigens. AD affects approximately 25% of children and 2% to 3% of adults. AD has a predilection for presenting in early childhood, with 60% of patients presenting within the first year of life and 90% present by 5 years of age.[2,3] A small percentage of individuals do have adult-onset AD, often presenting by 30 years of age; approximately 10% to 30% of individuals continue to have persistent AD into adulthood. Increased rates of adult-onset AD are seen in individuals who move from a more humid, tropical climate to a more temperate one located at higher latitude.

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Historically, AD has been referred to as the itch that rashes. Pruritus is a hallmark symptom of this disease and causes a significant effect on quality of life. Seventy percent of patients with AD have a positive family history of atopic disease, including other conditions, such as allergic rhinitis/rhinoconjunctivitis, food allergies, asthma, and environmental allergies. The odds of developing AD are 2 to 3 fold higher in a child with one atopic parent and 3 to 5 fold higher with 2 atopic parents.[4]

The atopic march describes the observation that patients with AD commonly go on to develop other allergic conditions, such as asthma and allergic rhinitis. Some estimates suggest one-third of children go on to develop asthma and two-thirds go on to develop allergic rhinitis.[5] More recent studies have also linked AD to other nonallergic conditions, the most compelling being attention-deficit/hyperactivity disorder.[6] Patients with AD have more irregular and altered sleep patterns at baseline as compared with individuals without AD. During flares of AD, rates of sleep disturbance are significantly increased and can affect entire families. Increased rates of depression and anxiety have also been noted in both teenagers and adults with AD.[7] Patients with AD are also more at risk for secondary complications, such as skin infections.

PATHOPHYSIOLOGY

The pathogenesis of AD is multifactorial and results from dysfunction of the skin barrier, dysregulation of the immune system, and environmental triggers. The dysfunction of the skin barrier can be genetically based with mutations in filaggrin (*FLG* gene).[8] Filaggrin plays a key role in epidermal differentiation and formation of the skin barrier, including the stratum corneum. The stratum corneum plays an important role in preventing transepidermal water loss and prevention of skin infections. Filaggrin also breaks down to the skin natural moisturizing factor, which aids in skin barrier function and hydration. In addition to a dysfunctional skin barrier, patients with AD also have dysregulation of their immune system. This dysregulation causes an upregulation of the T helper type 2 (Th2) pathway, impaired innate immunity, and increased allergic sensitization.

The hygiene hypothesis explains the increasing prevalence of AD and other allergic conditions. This theory postulates that improved hygiene decreases early life exposure to infectious agents. These infections exert their effect through the Th1 pathway. There is thought to be an inverse relationship between Th1 and Th2 pathways. Therefore, decreased infectious exposures leads to decreased Th1 activation and increased Th2 pathway activity. This shift to the Th2 arm of the pathway leads to increased allergic sensitization. Finally, environmental triggers also play a role in the development and propagation of AD. It has been shown that, in climates with higher humidity, increased mean temperatures, lower precipitation, decreased indoor heating, and higher ultraviolet light index, there are lower incidences of AD.[9]

PHYSICAL EXAMINATION

AD presents acutely as an erythematous and pruritic rash typically with ill-defined xerotic papules and plaques with scattered erosions and often with oozing and crusting. In more chronic cases, one can see lichenified and hyperpigmented plaques (**Fig. 1**). AD has an age-specific morphology and distribution that can change over time. In infants and young children (<2 years of age), we see a predilection for face (**Fig. 2**), neck, scalp, wrists, and extensor extremities (**Fig. 3**) and a higher incidence of exudative rash. These areas correlate with infants' activities (eg, crawling) and are areas that they are able to rub or scratch. This infantile pattern often disappears by 2 years of age. Classic flexural involvement of the antecubital and popliteal fossa

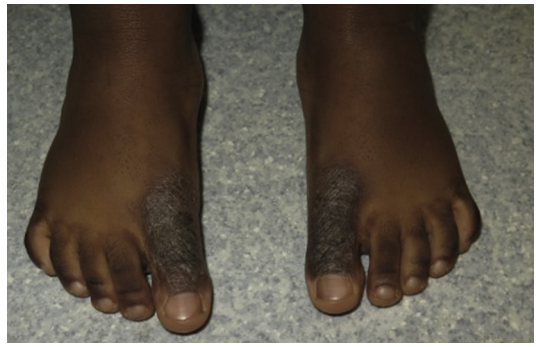

Fig. 1. Lichenified and hyperpigmented plaques.

(Fig. 4) can be seen at any age but tends to more often occur after 2 years of age. The rash during childhood tends to be less exudative and can also show predilection for the neck circumferentially, eyelids, and flexural wrists. In adolescents, there is classic flexural involvement but also common involvement of the forehead, periocular area (Fig. 5), and neck. In adults, AD localizes to specific areas of involvement, mainly the hands, feet, nipple, and eyelids with occasional generalized involvement in classic flexural areas. Lichenification and prurigo nodule development are more commonly seen in adolescent and adult patients with AD. Specific clinic findings to AD are nipple involvement and upper lip cheilitis (Fig. 6). Other clues to AD that help distinguish it from other conditions are the relative sparing of the groin, axilla, nasal tip, and diaper area. This distinction is largely caused by retention of moisture in these areas, presence of a protective covering, and the oily nature of the nasal tip. Xerosis and pruritus are universally present. Patients with AD may also have an impaired ability to sweat and may complain of increased pruritus related to exercise or heat. Other associated clinical features that can be seen in patients with AD are listed in Box 1.

DIAGNOSTIC TESTS/IMAGING STUDIES

AD is a clinical diagnosis that is made based on morphology, distribution of skin rash, historical features, physical examination, and clinical findings. Diagnostic criteria for AD have been proposed by Hanifin and Rajka[10] in 1980 but are difficult to use in clinical practice with 4 major criteria and 23 minor criteria. The American Academy of

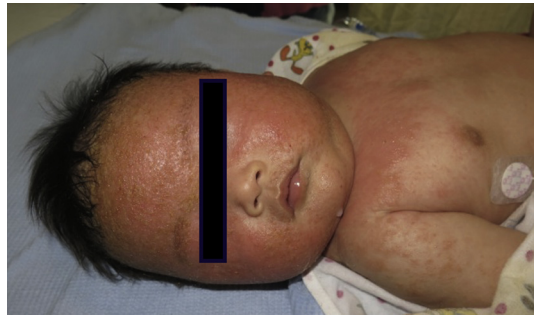

Fig. 2. Infant with face rash.

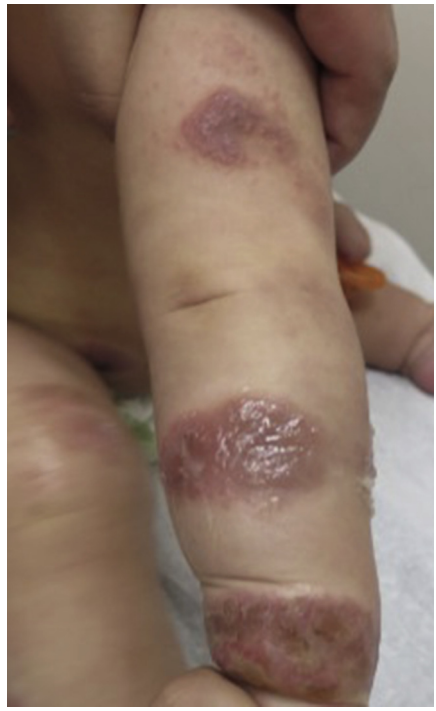

Fig. 3. Rash on extensor extremities.

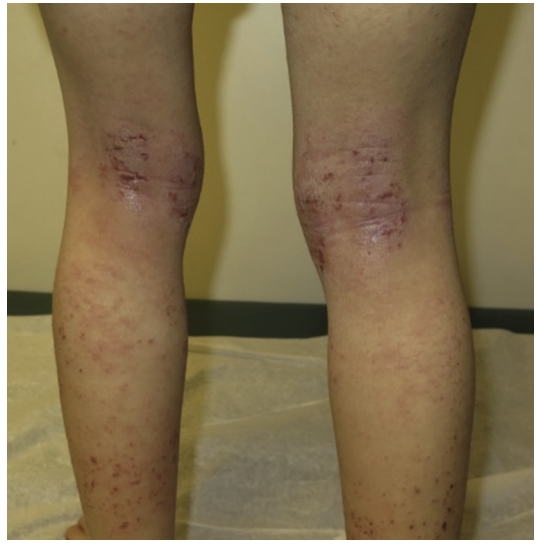

Fig. 4. Classic flexural involvement of the popliteal fossa.

Fig. 5. Rash on the forehead, periocular area.

Dermatology Consensus group and UK working group have revised the criteria making them more applicable to clinical practice. **Table 1** identifies the revised criteria.

Skin biopsy and other laboratory evaluations are used to rule out other diagnoses or confirm other associated skin disorders. There is currently no biomarker that is completely specific to AD. If serum testing is done, one can find AD associated with an elevation of total immunoglobulin E level or elevation of peripheral eosinophilia; but this is not uniformly present in every case. These laboratory findings do not correlate with disease severity and are not sensitive or specific to AD.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AD is broad (**Box 2**). There are a variety of nutritional and immunodeficiency disorders that present with eczema as a hallmark feature. There may be subtle morphologic clues in these cases, but in general a high level of suspicion is needed. Scabies can often be mistaken for AD. Scabies can be distinguished by evidence of burrows, which are thin tortuous gray lines often with a pustule or papule housing the mite at the end. In adults, the head and neck are often spared; there is a high predilection of rash in the interdigital web spaces, genital region, and umbilicus. In infants and children, the rash of scabies is polymorphic and widespread, with a predilection often for the palms and soles (**Figs. 7** and **8**); but the rash can be present anywhere. There are often other family members with a pruritic rash given that scabies is spread by close contacts. Psoriasis is an inflammatory skin disorder that is characterized by well-defined, often symmetric pink papules and plaques with overlying micaceous scale (**Fig. 9**). Psoriasis has a predilection for the scalp, nails, extensor surfaces of the limbs, umbilicus, and sacrum. It can often be distinguished from AD by its morphology. Psoriasis also tends to be less exudative and is not prone to superinfection. Seborrheic dermatitis can be distinguished from AD as it has a predilection for more oily and warm areas (eg, scalp, eyebrows, nasolabial folds, groin,

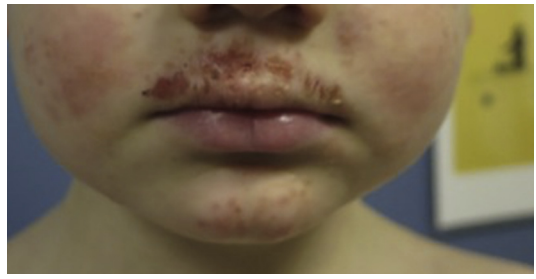

Fig. 6. Upper lip cheilitis.

Box 1
Other associated clinical features

Atypical vascular responses: facial pallor, white dermatographism, delayed blanch response

Keratosis pilaris

Hyperlinear palms

Ichthyosis vulgaris

Ocular and periorbital hyperpigmentation

Dennie-Morgan lines (prominent groove or line of the lower eyelid)

Perifollicular accentuation and lichenification (seen more in darker skinned individuals)

Lichenification

Prurigo nodules

Table 1
Diagnostic criteria for AD

Essential Features (Must Be Present)	Important Features (Seen in Most Cases, Adding Support to the Diagnosis)	Associated Features (These Clinical Features Help to Suggest the Diagnosis of AD but Are Too Nonspecific to Be Used to Define or Detect AD for Research or Epidemiologic Studies)	Exclusion of Other Conditions
1. Pruritus 2. Eczema (acute, subacute, chronic) a. Typical morphology and age-specific patterns i. Flexural lichenification in adults ii. Facial and extensor involvement in infancy b. Chronic and relapsing course	1. Early age of onset 2. Atopy a. Personal and/or family history b. Immunoglobulin E reactivity 3. Xerosis	1. Atypical vascular responses (ie, facial pallor, white dermatographism, delayed blanch response) 2. Keratosis pilaris/hyperlinear palms/ichthyosis 3. Ocular/periocular changes 4. Other regional findings (ie, perioral changes, periauricular lesions) 5. Perifollicular accentuation/lichenification/prurigo lesions	1. Scabies 2. Seborrheic dermatitis 3. Contact dermatitis (irritant or allergic dermatitis) 4. Ichthyoses 5. Cutaneous T-cell lymphomas 6. Psoriasis 7. Immune deficiency disorders 8. Tinea corporis

Data from Eicheifield LF, Hanifin JM, Luger TA, et al. Consensus conference on pediatric atopic dermatitis. J Am Aacd Dermatol 2003;49:1088–95.

Box 2
Differential diagnosis of AD

- Scabies
- Ichthyosis
- Seborrheic dermatitis
- Psoriasis
- Contact dermatitis
- Cutaneous T-cell lymphoma
- Nutritional deficiencies
  - Acrodermatitis enteropathica
  - Zinc deficiency (prematurity, deficient breast milk zinc, cystic fibrosis)
  - Gluten-sensitive enteropathy
  - Other nutritional deficiencies (biotin, essential fatty acids)
- Immune deficiency disorders
  - Hyper–immunoglobulin E syndrome
  - Severe combined immunodeficiency
  - Wiskott-Aldrich syndrome
  - Agammaglobulinemia
  - Netherton syndrome
  - Ataxia-telangiectasia
- Tinea corporis
- Langerhans cell histiocytosis

gluteal crease, umbilicus) because of its pathogenesis being linked to lipophilic yeast, *Pityrosporum ovale*. Seborrheic dermatitis has a yellow, greasy appearance on an erythematous base. The distribution and appearance can help distinguish this condition from AD. In infants, there is often overlap of these two conditions; therefore, it can be more difficult to distinguish them, but treatment in this age group is often similar for both conditions.

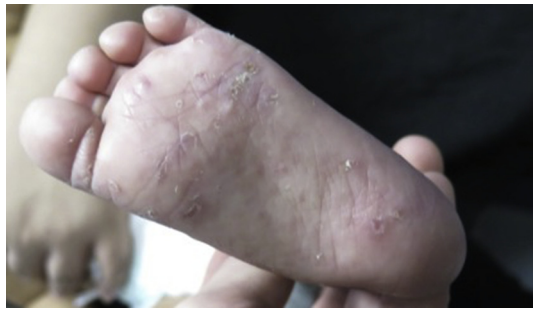

Fig. 7. Rash of scabies on the sole.

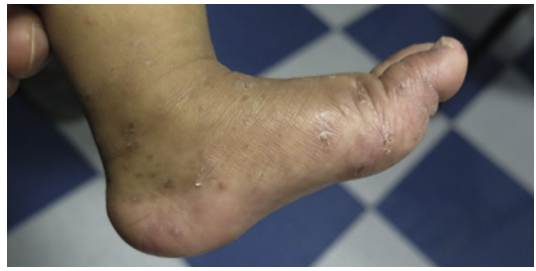

Fig. 8. Rash of scabies on the foot.

DIAGNOSTIC DILEMMAS

The diagnosis of AD is often made based on history and physical examination, but there can be some overlap with the conditions mentioned earlier. If there is diagnostic uncertainty, further testing can be done, such as skin biopsy, patch testing for allergic contact dermatitis, scabies scrapings, and laboratory evaluation to rule out other disorders. Skin biopsy or repeat skin biopsy should be considered when the rash is recalcitrant to adequate and appropriate therapy, progressing despite treatment, or patients have other positive review of systems or physical examination findings that are concerning.

TREATMENT

Treatment of AD often includes multiple modalities of therapy being used together, some of them being nonpharmacologic, to target different aspects of AD pathogenesis. Treatment and management of AD is to control symptoms of an acute flare but then to be proactive and minimize future relapses of the disease.

When treating an individual with AD, all of the following concerns should be assessed and addressed for optimal treatment and management:

1. Restore and maintain the skin barrier function
2. Minimize inflammation
3. Control pruritus
4. Consider and manage external environmental triggers
5. Treat infection

Restoring the Skin Barrier

Patients with AD have a defect in their skin barrier leading to greater transepidermal water loss and xerosis. There is very strong evidence that use of moisturizers is very beneficial to patients with AD.[11] Moisturizing decreases the amount of medication

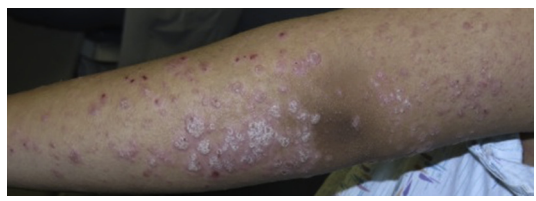

Fig. 9. Psoriasis papules and plaques with overlying micaceous scale.

used and symptoms of AD (ie, erythema, pruritus, skin fissuring). Moisturizers should be fragrance and dye free to limit possible irritants, and liberal and frequent application is recommended to prevent xerosis. Application of the moisturizers immediately after bathing can further improve skin hydration in patients with AD by sealing in moisturize from the bath. Moisturizing alone can be a treatment of mild disease and is a very important part of maintenance therapy and prevention of flares. The various formulations of emollients are listed in **Table 2**.

Antiinflammatories

Topical corticosteroids

Topical corticosteroids (TCSs) are the first-line treatment of AD and are a mainstay of therapy. They are grouped in 7 classes from very low potency (class 7) to high potency (class 1) and come in various strengths and formulations (**Table 3**). The choice of TCS is guided by location applied, severity of disease, extent of disease, availability, patient preference, and cost. A guide to the adequate amount of medication to be applied is approximately 0.5 g or an adult fingertip (from distal interphalangeal joint to distal fingertip) to 2 palms of rash (approximately 2% body surface area).

When choosing a TCS, the general principles to consider are thickness of the skin the medication will be applied to, body surface area affected, and if there will be occlusion of the medication. Lower-potency TCSs are recommended in thin skin areas (eg, face, neck, and genital area) and areas of occlusion (eg, skin folds and intertriginous areas) where there is increased absorption of medication and higher risk of skin thinning. Higher-potency TCSs should be used in thick-skin areas (eg, palms and soles) to penetrate the stratum corneum. When applying TCS to a larger body surface, higher-potency steroids should be avoided to prevent significant systemic absorption. Application of TCS is recommended twice a day and should be used until inflammatory lesions are significantly improved, which could be for several weeks at a time. There has been recent evidence suggesting that individuals who have frequent flares of disease in the same site can use a more proactive approach of applying TCS once to twice weekly to these areas as maintenance therapy to reduce rates of relapse and increase time between flares. This use of intermittent TCS has been shown to be more effective than moisturizers alone.[12]

Table 2
Emollient vehicles

Vehicle	Pros	Cons
Ointment	• Greatest moisturizing effect • Highest proportion of lipid • Free of preservatives, does not sting when applied	Greasy

Cream	• An emulsion of water in lipid
	  ○ More hydrating than lotions
	  ○ Less greasy
		Contains preservatives, can sting or burn with application

Lotion	• Emulsion of a higher proportion of water to lipid than creams • Well tolerated • Not greasy	May need increased applications to keep skin hydrated
Oil	• Easy to spread over a large surface area	Can contain some preservatives and fragrances that could be irritating
Gel	• Not appropriate for AD	Drying

Table 3
TCS formulations by class

Class	Medication	Strength (%)	Form
I. Superpotent	Augmented betamethasone dipropionate	0.05	Ointment
	Clobetasol propionate	0.05	Ointment, cream, solution, foam
	Diflorasone diacetate	0.05	Ointment
	Fluocinonide	0.1	Cream
	Halobetasol propionate	0.05	Ointment, cream
II. High potency	Betamethasone dipropionate	0.05	Ointment, cream, foam, solution
	Budesonide	0.025	Cream
	Desoximetasone	0.25	Ointment, cream
	Diflorasone diacetate	0.05	Cream
	Fluocinonide	0.05	Ointment, cream, and gel
	Halcinonide	0.1	Ointment, cream
	Mometasone furoate	0.1	Ointment
	Triamcinolone acetonide	0.5	Ointment, cream
III–IV. Medium potency	Betamethasone valerate	0.1	Ointment, foam
	Clocortolone pivalate	0.1	Cream
	Desoximetasone	0.05	Cream
	Fluocinolone acetonide	0.025	Ointment, cream
	Flurandrenolide	0.05	Cream
	Fluticasone propionate	0.005	Ointment
	Mometasone furoate	0.1	Cream
	Triamcinolone acetonide	0.1	Ointment, cream
V. Lower-medium potency	Hydrocortisone butyrate	0.1	Ointment, cream, solution
	Hydrocortisone probutate	0.1	Cream
	Hydrocortisone valerate	0.2	Ointment, cream
	Triamcinolone acetonide	0.25	Ointment, cream
VI. Low potency	Alclometasone dipropionate	0.05	Ointment, cream
	Desonide	0.05	Ointment, cream
	Fluocinolone acetonide	0.01	Cream, oil, solution
	Flurandrenolide	0.025	Cream
VII. Lowest potency	Dexamethasone	0.1	Cream
	Hydrocortisone	2.5	Ointment, cream, lotion
	Hydrocortisone acetate (over the counter)	0.5 and 1.0	Cream, ointment

Overall, TCSs have a good safety profile with low adverse effects reported.[13] Most of the side effects reported are cutaneous but are uncommon with proper use. The cutaneous side effects include purpura, telangiectasias, striae, focal hypertrichosis, and acneiform and rosacealike eruptions. The highest risk of developing adverse cutaneous effects are with application of TCS in sites of occlusion and thinner-skin areas, use of higher potency TCS, and use of TCS in older patients with thinner skin. Most cutaneous side effects are reversible after stopping TCS but may take months to resolve. Patients can also develop an allergic contact dermatitis or type 4 hypersensitivity reactions to TCS themselves or to the ingredients within the formulation. It is important to consider this if a rash worsens or fails to respond to TCS and perform patch testing to determine the exact allergen.

Systemic side effects with TCS use, such as hypothalamic-pituitary-adrenal (HPA) suppression, are extremely low.[14] The risk of HPA suppression increases in children who have a high body surface area to weight ratio, individuals receiving other forms of corticosteroids (eg, inhaled, oral, and intranasal), and with prolonged and continued use of high-potency TCS. If there is a concern for HPA axis suppression, a cortisol stimulation test should be performed to assess adrenal response. Other systemic side effects, such as hyperglycemia and hypertension, have been rarely reported.[15] The risk of development of cataracts and glaucoma with TCS use has been unclear with current studies. One reason for this is about 10% of patient with AD develop cataracts as a secondary manifestation of their disease, and these cataracts are indistinguishable from cataracts induced by corticosteroids. Given this uncertainty, it is recommended to limit long-term periocular use of TCS and switch to a topical calcineurin inhibitor (TCI) if a long-term antiinflammatory is needed.

Some patients or parents of patients have a phobia of using corticosteroids, which can significantly interfere with the treatment of AD. These concerns should be addressed directly with patients and families to address any misunderstanding about the medications.[16]

Topical calcineurin inhibitors

TCIs are steroid-sparing agents that can be used in conjunction with TCS or by themselves. They are derived from the *Streptomyces* bacteria and inhibit T-cell activation, thereby blocking proinflammatory cytokines and mast cell activation. The various formulations of TCI are listed in **Table 4**. TCIs do not have the cutaneous adverse side effects that TCS have. Their use is indicated when there is evidence of steroid-induced atrophy, in areas at high risk for skin thinning, and when TCSs have been used continuously long-term. Like TCSs, TCIs can also be used as a maintenance therapy 1 to 3 times per week to prevent flares at recurrent sites of disease. Side effects of TCI include local reactions of burning and stinging. These side effects are more widely reported with TCIs than TCSs. These reactions tend to decrease over time. Use of TCSs before TCIs can also decrease sensations of burning and stinging. TCIs are not to be used when there is active infection according to the package insert; but no consistent increase in viral infections have been noted, and there has been some evidence to show a decrease in staphylococcal aureus colonization. There is also a black box warning for TCI regarding a theoretic risk of malignancy (ie, skin cancer and lymphoma). This warning is based on animal studies and is not directly

Table 4
TCSs

Medication	Pimecrolimus 1%	Tacrolimus 0.3%	Tacrolimus 0.1%
Vehicle	Cream	Ointment	Ointment
FDA approved	• Mild to moderate AD • >2 y of age[a]	• Moderate and severe AD • >2 y of age[a]	• Moderate and severe AD • >15 y of age
TCS equivalent	No direct comparison study done; thought to be low–mid potency	Low–mid potency	Midpotency

Abbreviation: FDA, Food and Drug Administration.

[a] Studies have shown effective and safe use in children less than 2 years of age.

Data from Breuer K, Werfel T, Kapp S. Safety and efficacy of topical calcineurin inhibitors in the treatment of childhood atopic dermatitis. Am J Clin Dermatol 2005;6:65–77.

translatable to humans. There is currently no evidence for a causal relationship between TCI use and malignancy.[17]

Phototherapy

When patients fail optimal topical therapy, then the next step in treatment can be phototherapy or system medications. Phototherapy is the use of light waves for the treatment of medical conditions. There are various types of phototherapy including narrowband UVB (NBUVB), broadband UVB, UVA, topical and systemic psoralen plus UVA (PUVA), UVA and UVB, and Goeckerman therapy, which uses crude coal tar in combination with phototherapy. NBUVB is the most widely used and available form of phototherapy. Treatment protocols are in place for the treatment of AD with each specific type of phototherapy that are based on the minimal erythema dose and Fitzpatrick skin type. Phototherapy can be used as a monotherapy or in conjunction with emollients and TCS, but the use of phototherapy with calcineurin inhibitors is cautioned. Patients' personal and family history of skin cancer should be taken into account when determining if phototherapy is the best modality of treatment of an individual because of the increased actinic damage and potential risk of developing a skin cancer, though this risk is low. Also, patients should be counseled regarding the use of topical or systemic photosensitizing medications with use of phototherapy. The side effects of phototherapy that are more common include actinic damage, local erythema, tenderness, burning, pruritus, and stinging. Less commonly nonmelanoma and melanoma skin cancers can develop, but this is seen more with the use of PUVA or UVA.[18] The main barriers to phototherapy are cost, availability, time, and the logistical challenge of treatments 2 to 3 times per week. Home phototherapy units are also available and can be used under practitioner guidance but can be costly and difficult to obtain.

Systemic immunosuppressants

The most commonly used systemic immune-modulating medications used for AD are azathioprine, cyclosporine, mycophenolate mofetil, and methotrexate.[19] These medications have been recommended for the treatment of refractory AD when optimal topical treatments and/or phototherapy has been ineffective (**Table 5**). These agents are all steroid-sparing agents, and their use is off label for AD. The use of oral corticosteroids in AD should be avoided if possible. Oral corticosteroids only temporarily suppress disease, and short courses often lead to flares of the AD once medication is withdrawn. Corticosteroid use should be reserved for acute and severe flares of AD where a short course of corticosteroids can act as a bridge to a steroid-sparing systemic medications or phototherapy that may take a longer time to take effect.

Management of pruritus

Patients with AD have a significant component of pruritus that significantly affects their quality of life. Pruritus in AD is driven by the release of histamine from basophils and mast cells. Pruritus causes significant sleep disturbance as well as difficulty in concentration during the day in school or work for patients. Various topical and oral medications have been suggested to address pruritus. Topical antihistamines are not recommended, as they are not effective at controlling pruritus or inflammation and may cause burning and stinging. Use of intermittent sedating oral antihistamines is more effective at controlling pruritus related to AD and should be used in conjunction with other antiinflammatory treatments for AD and emollients. The intermittent use of a sedating antihistamine at night can be beneficial in decreasing pruritus and helping improve sleep patterns; but its effect on routine activities and school and work performance should be considered when dosing and scheduling medications. The use of

Table 5
Systemic medications for AD

Medication	Pros/Cons	Contraindications	Management Guidelines
Azathioprine	Pro: • May be more favorable long-term based on side-effect profile Cons: • Slower onset of action than CSA • Weeks to 2 mo until treatment effect noted • Risk of bone marrow suppression	Absolute: • Allergy to azathioprine • Pregnancy or attempting pregnancy • Active infection Relative: • Concurrent use of allopurinol • Live vaccines may be contraindicated	• Requires baseline TPMT activity to determine dosing • TPMT is an inducible enzyme, levels of azathioprine can be altered over time • Pregnancy category D
Cyclosporine	Pros: • Rapid onset of action • Significant decrease in disease activity noted within 2–6 wk of initiation • Shown to be effective in inducing remission of disease Cons: • Risk of malignancies (eg, cutaneous and lymphoproliferative) • Potential long-term adverse effects of renal dysfunction and hypertension	Absolute: • Abnormal renal function • Malignancy • Uncontrolled hypertension • Hypersensitivity to cyclosporine • Live vaccines contraindicated; killed vaccines may have decreased efficacy Relative: • Poorly controlled diabetes • Major infection • Concomitant use of PUVA, UVB, MTX, other immunosuppressant agents, coal tar	• FDA approved for use up to 1 y • Therapeutic in both 1-y continuous dosing and 3–6 mo intermittent courses • High rates of potential medication interactions (CYP3A4) • Quicker onset of action with microemulsion formulation • Should be administered in BID dosing • Pregnancy category C
Methotrexate	Pros: • Easily available • Can be given weekly • Well-known side-effect profile Cons: • Slower onset of action than CSA • Risk of malignancies (cutaneous and lymphoproliferative)	Absolute: • Pregnancy • Nursing mothers • Alcoholism • Alcoholic liver disease • Chronic liver disease • Immunodeficiency • Bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia • Hypersensitivity to MTX Relative • Abnormalities in renal or liver function • Active infection • Obesity • Diabetes mellitus • Live vaccines may be contraindicated	• Possible liver biopsy at 3.5–4.0 g cumulative dose, but studies lacking if this is needed in patients with AD • Folic acid supplementation may skip on day taking MTX • Pregnancy category X

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Table 5
(*continued*)

Medication	Pros/Cons	Contraindications	Management Guidelines
Mycophenolate mofetil	Pros: • Favorable side-effect profile • Well tolerated • Longer clinical remission in some studies once medication was discontinued Cons: • Delayed onset of action • Insufficient data exist in regard to MMF and AD • Risk of malignancies (cutaneous and lymphoproliferative)	• Hypersensitivity to MMF and mycophenolic acid • Pregnancy or attempting pregnancy • Live vaccines may be contraindicated	• Pregnancy category D

Abbreviations: CSA, cyclosporine; FDA, Food and Drug Administration; MMF, Mycophenolate Mofetil; MTX, Methotrexate; TPMT, thiopurine methyl-transferase enzyme.

nonsedating antihistamines has not routinely shown to cause significant improvement in pruritus related to AD at standard doses. Rather, nonsedating histamines are more beneficial when urticaria is present on examination, when there is an identified environmental allergen trigger, or with a concomitant allergic condition (ie, allergic rhinitis, seasonal allergies.)

External environmental factors

Patients with AD have higher rates of sensitization to house dust mites, pollens, animal dander, and fungi. The relationship between AD and food allergies is cause for many questions and concern from patients. Patients with AD have increased rates of food allergies, but true food allergy-induced AD is rare. Food allergies as a cause of AD are most common in children less than 5 years of age. The National Institute of Allergy and Infectious Disease Food Allergy Expert Panel recommends consideration of allergy testing in individuals less than 5 years of age when (1) AD continues to be persistent despite optimized and appropriate treatment of AD, (2) reliable history of immediate allergic reaction after ingestion of a specific food, or (3) both. In older children and adults, food allergies tend to be less common. In these groups, allergy testing should be pursued if there is a reproducible history of a certain allergen causing AD flares. Testing should be dictated by a reproducible allergen or allergens that are most prevalent in a given population based on age. In children less than 5 years of age, common allergens include cow's milk, eggs, wheat, soy, and peanuts. In this age group, allergens should be retested over time as individuals can build tolerance and outgrow these allergies. In older children, tree nuts, shellfish, and fish are more common allergens. In adolescents and adults, pollen-related food allergies are more common, so individuals experience symptoms when eating certain foods if they are allergic to certain types of pollen. When performing allergy testing, either food-specific immunoglobulin E serum testing or skin prick testing, it is important to know that both tests have a high negative predictive value of greater than 95% and

low positive predictive value of 40% to 60%. Negative test results are helpful to rule out food allergies, but positive tests signify sensitization and not always true allergy. Therefore, clinical correlation and history are very important to help confirm the true presence of an allergy. Another environmental trigger for AD is the house dust mite, *Dermatophagoides pteronyssinus*. Dust mite covers for pillows and mattresses can be used to decrease exposure, but evidence is limited supporting their overall effectiveness. Seasonal allergies can sometimes exacerbate AD; in these cases, the use of nonsedating antihistamines can be helpful in conjunction with AD management.

Skin infection

Patients with AD are more prone to skin infections because of impaired skin barrier, diminished immune recognition, and impaired antimicrobial peptide production. Patient with AD also have increased amounts of *Staphylococcus aureus* colonized on their skin: 76% to 100% in patients with AD compared with 2% to 25% in healthy controls. This colonization can be a driving force for increased inflammation and pruritus.[20] In addition to increased susceptibility to bacterial infections, patients with AD can also be prone to superinfection with viral pathogens, such as herpes simplex virus (eczema herpeticum), varicella, and recently a new strain of the Coxsackie virus A6 (eczema coxsackium).[21] Patients with AD may also develop extensive molluscum contagiosum and flat warts, which can be difficult to clear. These infections can spread quite rapidly and be severe because of the disrupted skin barrier.

The approach to combating bacterial superinfection in AD has 2 prongs: one aimed at treating current infection and second with decreasing bacterial colonization to prevent future infection. Application of topical antimicrobials to treat infection has not shown to have a clear benefit and can cause contact dermatitis and promote antimicrobial resistance. Therefore, they are not recommended in treatment of AD. Systemic antibiotics can be used when there is clinical evidence of bacterial infection and can be used in conjunction with TCS. It is recommended to document infection by culture and antibiotic sensitivity testing, confirming the type of bacteria present and any resistance patterns and serving as a helpful to guide to direct therapy. Application of mupirocin 2% ointment twice daily intranasally for the first 5 days of every month for 3 months has shown some effect in decreasing *Staphylococcus aureus* colonization when used in conjunction with dilute bleach baths. Dilute bleach baths (sodium hypochlorite) also solely have been effective for decreasing *Staphylococcus aureus* colonization.[22] Studies have also shown sodium hypochlorite to have antiinflammatory properties regulated through the inhibition of 2 important genes of nuclear factor-kB, which regulates the inflammatory response in the skin.[23] The concentration of sodium hypochlorite is 0.25 to 0.5 cups of 6% sodium hypochlorite to a bathtub of water (40 gallons) = 0.005%. Bleach baths can be used for maintenance therapy for individuals with recurrent bacterial infections. There is no optimal guideline for frequency of baths, but some recommendations are from 1 to 3 times per week. Dilute bleach baths are overall well tolerated; but if patients have numerous eroded areas, they can experience some stinging; therefore, it may be best to start bleach baths a few weeks after the acute flare of AD has subsided. If taking a bath is not possible or patients do not have a bathtub, other possible options to decrease bacterial colonization are using a spray bottle of dilute bleach in the shower or using chlorhexidine soap 4%. Chlorhexidine does have antimicrobial properties but does not have the antiinflammatory effects of sodium hypochlorite. It can also potentially be an irritant dermatitis.

Eczema herpeticum is more frequently seen in children and is secondary to transmission of herpes simplex virus (HSV)-1 often by a parent or caregiver. Once infected with HSV, patients with AD can have recurrent episodes of eczema herpeticum that

presents with the appearance of sudden crusted, vesicular, eroded, and punched out papules in previous areas of AD. If there is periorbital involvement, an ophthalmologic evaluation is recommended to rule out the possibility of herpetic keratoconjunctivitis. Secondary bacterial infection in the setting of eczema herpeticum is common, so treatment with oral antivirals and oral antibiotics is warranted in this scenario. This treatment is in conjunction with use of TCS and optimal skin-directed management of AD. If an individual has recurrent episodes of eczema herpeticum, antiviral prophylaxis can be considered.

OTHER MANAGEMENT CONSIDERATIONS

In addition to the various treatments outlined earlier, there are other nonpharmacologic interventions that practitioners taking care of patients with AD should understand. Bathing is an important component to address in patients with AD. Once-a-day bathing for a maximum of 5 to 10 minutes in warm (not hot) water, with use of fragrance- and dye-free nonsoap cleansers, and application of an emollient immediately afterward to prevent drying out of the skin are recommended. Soap use can be harmful to the stratum corneum and can cause further irritation and damage to the skin barrier. Bath additives and water-softening devices have not shown any benefit to AD. Wet wraps are also an important therapeutic intervention that can be used in recalcitrant disease or during a severe flare of AD to improve penetration of topical medications, help heal the skin by providing a barrier from repeating traumatization, and decrease transepidermal water loss. Wet wraps consist of applying a topical agent (emollient +/- medication) to the skin and applying a wet first layer (eg, gauze, tubular bandages, cotton suit) that is damp and wrung out followed by a dry second layer. Use of TCS rather than just emollients has shown to be a more effective therapy. The easiest method for patients to do this is to apply 2 layers of nonirritating cotton clothing, one as the wet layer and the second as the dry layer. Wet wraps can be used for a few days up to 2 weeks and can be worn from a few hours to 24 hours. Often they are best tolerated and easiest for patients when worn overnight. Strength of TCS being used and the body surface area that it is being applied to should be considered carefully to prevent skin atrophy or increased systemic absorption. The risk of HPA suppression is very low with short courses of wet wrap therapy, once-a-day use, and use of lower to midpotency TCS for larger body surface areas.

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