CLINICAL MANAGEMENT extra

Diagnosis and Management of Atopic Dermatitis: A Review

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GENERAL PURPOSE:

The purpose of this learning activity is to provide information about the diagnosis and management of atopic dermatitis (AD).

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After completing this continuing education activity, you should be able to:

1. Recall the diagnostic process of AD.
2. Identify nonpharmacologic therapies for skin care in patients with AD.
3. Explain the pharmacologic management of AD.

ABSTRACT

Atopic dermatitis is a chronic, relapsing, intensely pruritic inflammatory skin disease that affects both children and adults. This article provides an overview of the epidemiology, clinical features, pathophysiology, complications, and specific investigations of atopic dermatitis. The current and novel therapies for the treatment of atopic dermatitis will be discussed.

KEYWORDS: atopic dermatitis, atopy, eczema, inflammatory skin disease, pruritus, skin disease

ADV SKIN WOUND CARE 2018;31:538–50.

CASE STUDY

A 3-month old boy was referred to dermatology for uncontrolled eczema. His parents described dry erythematous patches of skin that began when he was 4 weeks old. They had been using 1% hydrocortisone cream on the body and betamethasone 0.1% lotion on the scalp. Three weeks prior to presentation, the child had been prescribed a 2-week course of systemic cephalexin and topical mupirocin cream 2% for impetiginized eczema, but it had not improved.

His medical history was otherwise unremarkable, being born full term by vaginal delivery with an uncomplicated postnatal course. There were no concerns with his height, weight, or developmental milestones to date, and immunizations were up to date. There was a history of rhinitis in the father and mild dermatitis in his 2-year-old brother, but no other history of atopy in the family.

On examination at presentation, there were scattered nummular patches of dermatitis with some erosions and crusting over the torso and extremities (Figure). He had scattered erythematous papules on his face and thick adherent yellow scale on greater than 40% of the scalp. He was afebrile.

At the first visit, education was provided on the natural history and management of atopic dermatitis (AD), and handouts provided with links to eczema information websites. The family was instructed to bathe the child one or two times daily in lukewarm water for 5 to 10 minutes using a mild, unscented cleanser. After drying gently, they were advised to apply prescription ointments to eczema patches and a bland emollient to the rest of the body.

For the patient's current flare, betamethasone valerate 0.1% ointment was prescribed for application twice daily to dermatitic patches on the body, and hydrocortisone valerate 0.2% ointment was prescribed for the boy's face. Betamethasone valerate 0.1% lotion was continued for use on the scalp. Swabs were taken of the crusted patches on the body to assess for methicillin-resistant *Staphylococcus aureus*. Sulfamethoxazole-trimethoprim was prescribed twice daily for antistaphylococcal coverage as well as anti-inflammatory action. Hydroxyzine syrup was prescribed as needed for sleep and itch.

Adjunctive measures were reviewed with the family; cotton clothing and bed sheets were recommended, as well as using mild detergents or plain vinegar for washing without fabric softeners or dryer sheets. Follow-up was booked for 4 weeks, and the family was advised to call if there were any signs of infection.

INTRODUCTION

Atopic dermatitis is a chronic, relapsing, intensely pruritic inflammatory skin disease. This skin disease is commonly associated with allergic rhinitis (hay fever or seasonal allergies) and asthma. This triad of conditions is collectively known as *atopy*, with affected individuals having a personal or family history of one or more of the three conditions. This word was first used in 1923 to define a domain of inherited hypersensitivity to environmental allergens, disparate from hypersensitivity and anaphylaxis to infection.[1] It is commonly referred to by dermatologists as either AD or atopic eczema, and the terms can be used interchangeably.

In 1979, Hanifin and Rajka[2] advanced major criteria for the diagnosis of atopic eczema. Spearheaded by Williams et al[3] in 1993, a team of dermatologists and pediatricians formulated and validated diagnostic criteria for AD that closely paralleled the major criteria advanced by Hanifin and Rajka[2] with a further slight modification in 2005 by Williams[4] (Table 1).

EPIDEMIOLOGY

The lifetime prevalence of AD is estimated to be 10% to 30% in children and 2% to 10% in adults, with a two- or threefold

Figure.

NUMMULAR LESIONS ON THE POSTERIOR LEGS OF AN INFANT WITH ATOPIC DERMATITIS

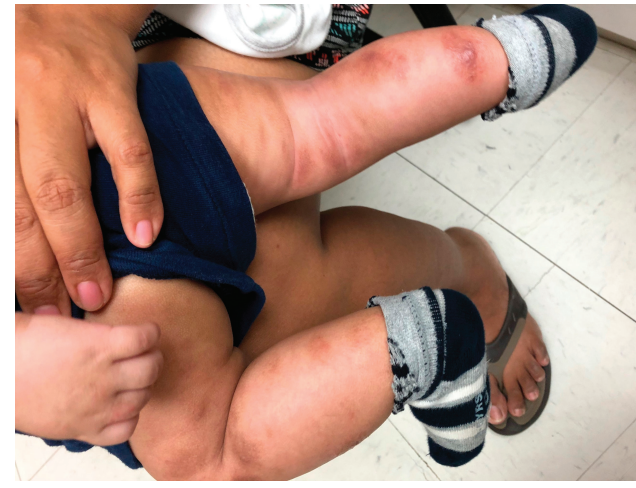


Table 1.
DIAGNOSTIC GUIDELINES FOR ATOPIC DERMATITIS[3,4]

Must have

- an itchy skin condition (or parental report of scratching or rubbing in a child)

Plus three or more of the following:

- History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, the neck, and around the eyes*
- A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4 years)
- A history of generally dry skin in the last year
- Visible flexural eczema (or eczema involving the cheeks/forehead and extensor limbs in children under 4 years)
- Onset under 2 years (not used if child is younger than 4 years)

*Original 1994 guidelines also included the cheeks in young children

increase over the past 3 decades in industrialized nations.[5] The International Study of Asthma and Allergies of Childhood (ISAAC) has provided the most salient trends of AD across the world; AD in general is not increasing or has leveled off in countries with the highest prevalence (eg, the United Kingdom). The younger children subpopulations (aged 6–7 and 13–14 years) and individuals in low-income countries are still experiencing an increased incidence of AD.[6,7] Research studies documented that a higher risk of AD development is associated with areas of industrialization, urbanization, and higher affluent class,[8–10] whereas living in more tropical latitudes and rural areas are associated with lower risk of AD.[11]

CLINICAL FEATURES

As documented in Table 2, pruritus, dry skin, and a compromised barrier function are characteristic of all stages of AD. Fish-like polygonal scales may appear on the skin, particularly the legs. These scales often spare the palms and soles and may be indistinguishable from ichthyosis vulgaris.

A decreased skin barrier can also facilitate microorganism overgrowth with bacteria, viruses, and yeasts. There is an increased susceptibility to secondary bacterial colonization and infection with staphylococcus more frequently than streptococcus, often presenting with crusting of involved skin with secondary impetiginization.

Hair follicles are often prominent on the extensor aspect of the upper arms and anterior thighs with a surface scale and underlying follicular prominence (keratosis pilaris), occasionally involving the cheeks. Pigmented skin (black or brown) may have a predominant follicular pattern that can also be present on the trunk as well as the rest of the body.

The area around the eyes may also offer clues for atopy. Allergic sensitivity often causes swelling of the periorbital skin that can leave shiners or dark skin with resolution. There is also often a double crease around the eye (Dennie-Morgan lines) or loss of the lateral third of the eyebrows from constant scratching. Increased skin markings may also be present on the neck and palms of the hands.

Atopic eczema may have a slight hypopigmented characteristic (pityriasis alba) that is common on the face of children. External stroking of the skin can produce white dermatographism especially over the scapular area where prestored mediators including histamine are not depleted.

There are three stages of AD based on the age of affected individuals (Table 3). The infantile stage is often acute, with papules (raised lesions <1 cm) that develop after the second week of life up to age 2 years. It is classically located on the head and neck with involvement of the extensor skin on the elbows and knees related to the trauma from the crawling posture. The infantile stage from age 2 years to puberty is most likely to present with subacute lesions on the trunk and extremities and prominent flexural involvement of the elbows and knees. The adult stage may be limited to the hands but can be involved elsewhere on the skin surface.

There are myriad regional expressions of AD that can be observed in patients because of dry skin and susceptibility to contact irritant or allergic dermatitis on the lips, ears, and eyelids. Changes in skin color may also reflect involvement of the skin with a yeast, *Malassezia furfur*. The yeast is a normal colonizing organism on the skin. When it overgrows and stimulates tyrosinase, an enzyme in melanocytes, it causes hyperpigmentation. Inhibition of tyrosinase leads to hypopigmentation and irritation of the skin can cause involved skin to be red. The hands and feet are often involved with acute, subacute, or chronic signs of eczema.

Nummular eczema (coin-shaped lesions) is most common on the arms and legs. This form of eczema is common in children with atopy and may be associated with contact allergic dermatitis, especially in adults. Not all persons with nummular eczema have atopy.

PATHOPHYSIOLOGY

The pathophysiology of AD is complex and multifactorial; AD is the product of the interaction between skin barrier dysfunction, immunologic factors, and environmental factors. Abnormal gene(s) that encode defective skin barrier components (eg, filaggrin, ceramides) lead to increased transepidermal water loss and associated dry skin and surface pH changes. The pathogenesis of AD is also orchestrated through a biphasic inflammatory response typified by a helper T-cell type 2 (TH2)

Table 2.
CLINICAL SIGNS AND SYMPTOMS OF ATOPIC DERMATITIS

Clinical Sign	Description
Pruritus	The unpleasant sensation of the skin that provokes the urge to scratch; it is the primary hallmark of atopic dermatitis. Scratching the skin can aggravate existing dermatitis, causing excoriations that are either linear or punctate. Skin becomes leathered, rough, hard, and thickened upon scratching.
Xerosis	Dry skin in areas without clinically apparent inflammation. More common during periods of low humidity (eg, winter) and primarily affects the legs. Dysfunctional epidermal barrier function leads to dehydration of the stratum corneum layer that should have a 10% moisture content.
Ichthyosis vulgaris	Fish-like dry scales that can often look extremely thick and dry. Affected patients may alternately have excessively thin, whitish to brown scaling that classically affects the lower legs and shins while sparing the flexures. It is inherited in an autosomal semidominant manner.
Keratosis pilaris	Patients will have thick scale and redness around the hair follicles that may be surrounded by a patchy erythema. This condition most frequently affects the lateral cheeks, extensor (outer) aspect of the upper arms, and anterior thighs. The onset is typically during childhood and can persist into adulthood.
Follicular prominence	Follicles have a goose-bump appearance. Most commonly seen on the trunks of children and in darker-skinned individuals of any age.
Palmar and plantar hyperlinearity	Patients more often have exaggerated palmar hand creases than plantar creases.
Dennie-Morgan lines	Also known as atopic pleats, this refers to dark, symmetric, double horizontal folds below the lower eyelids as a consequence of intermittent edema of the eyelids.
Periorbital darkening ("allergic shiners")	Refers to gray to violet-brown discoloration and swelling around the eyes because of intermittent edema and rubbing of the region
Anterior neck folds	Horizontal folds or lines across the middle of the anterior neck.
Hertoghe sign	Loss of the lateral third of the eyebrows because of constant scratching.
White dermatographism	A blanching response as a result of stroking of the skin with the back of a fingernail that leads to white streaks. This reaction reflects excessive capillary vasoconstriction and local edema. This sign is reproduced in the scapular area where histamine is not depleted with trauma as a prestored mediator.
Pityriasis alba	Consists of multiple ill-defined light (hypopigmented) patches with fine scaling that are often located on the face and neck and occasionally appear on the shoulders and arms. These lesions are most obvious in darkly pigmented individuals and/or following sun exposure. This condition mostly affects children and young adults.

lymphocyte-dominant response with overproduction of TH2 cytokines interleukin 4 (IL-4), IL-5, and IL-13 prior to converting to a T1 response.

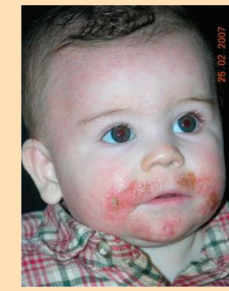
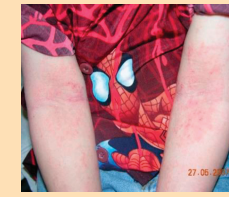
Finally, the interplay of psychological stress and environmental factors has a salient role in causing AD. The dysregulation of the skin barrier predisposes individuals to colonization of microbial pathogens. Well-established triggers for atopic eczema include environmental aeroallergens (eg, animal dander), along with environmental stressors such as reduced humidity and lower outdoor temperatures. Further, the use of harsh alkaline detergents and soaps over the skin is known to alter the skin's acidic pH. When the skin becomes more alkaline, this dysregulates downstream enzyme activity and triggers AD. A proper understanding of how the genetic, immunologic, and environmental factors interact with one another can help healthcare providers develop effective therapeutic management plans.

Microbial Colonization in Atopic Dermatitis

Patients with AD and their associated epidermal barrier dysregulation are at risk of skin infections with *S aureus* and *Streptococcus pyogenes*.[13–15] Approximately 90% of AD lesions have *S aureus* with methicillin-resistant *S aureus* colonization occurring in up to 12% of patients.[14]

Eczema herpeticum (widespread cutaneous herpes simplex virus infection) is a serious comorbidity occasionally seen in patients with AD.[16] Fungal infections also are commonly seen in patients with AD. In particular, the yeast *M furfur* commonly affects the head neck and trunk[17] with red, hypopigmented (white),

Table 3.
CLINICAL FEATURES BY AGE

Age Variant	Clinical Features	Figure
Infantile onset Not present at birth but onset between 2 wks & 2 y of age	Acute lesions of eczema: pruritic papules and vesicles with associated serous exudate or crusting Classical areas: head and neck Starts as scaling and erythema on the cheeks and extending into the neck, forehead, and scalp Crusting and lichenification (thickened skin with increased surface markings), secondary to scratching and rubbing of the involved areas Tends to involve extensor surfaces (trauma from crawling) rather than flexural surfaces	
Childhood onset Age 2 y to puberty	Lesions are dry and there are lichenified papules and plaques. Classical areas: wrist, ankles, hands, feet, antecubital and popliteal fossae (attributable to moisture and friction with upright walking) Facial involvement is less prominent, but when present, it is observed in a perioral and periorbital distribution Some children have a predominant extensor involvement Children of African ancestry have a more papular and follicular-based appearance	
Adult onset postpuberty	Onset begins from puberty and continues into adulthood Lesions are symmetrical, dry, scaly papules and plaques Lichenification and excoriations are common Crusting and exudation are less common Classical areas: predominantly flexural, in addition to the face, neck, and distal extremities. Older adults may present with involvement in the hand, nipple, or eyelid	

or hyperpigmented (light to medium brown) patches that may have a fine surface scale.

COMPLICATIONS

The patient burden of AD is significant. Itch and pain are the most commonly reported symptoms and can lead to detrimental effects on quality of life in both children and adults.[18] Itch can impact the ability to fall asleep and lead to frequent awakenings, resulting in decreased amount and quality of sleep. Children may be teased or bullied and feel self-conscious about their skin. This may also result in decreased participation in sports or leisure activities. Effective treatments often result in objective improvements in quality of life.[18]

DIAGNOSIS

A punch skin biopsy may be necessary for patients with atypical presentations to rule out other skin conditions that may resemble AD. These conditions include other inflammatory dermatoses (seborrheic dermatitis, psoriasis, allergic or irritant contact dermatitis, and pityriasis lichenoides), primary ichthyosis, infestations (scabies), infections (fungal, human immunodeficiency virus [HIV]), malignancies (most commonly cutaneous T-cell lymphoma), and metabolic disorders.[19] One needs to consider mycosis fungoides in patients with a skin eruption that may resemble AD presenting much later in life or that is completely resistant to therapy. Serial biopsies may need to be performed for a definitive diagnosis if there is a high index of suspicion. If HIV is suspected, a serum enzyme-linked immunosorbent assay for HIV should be performed.

Patients with extensive skin disease or recurrent staphylococcal infections may have very high levels of immunoglobulin E (IgE), and this should be measured in these patients. Bacterial skin swabs should be performed on crusted and persistent skin lesions and tested for culture and sensitivity. Chronic staphylococcal carriage

in the nostrils or perianal skin may also be a source of recurrent staphylococcal infections.

There may also be a history of IgE-mediated food allergies. Food allergy testing for moderate to severe AD patients younger than 5 years of age should be performed with a reliable history of immediate reaction after ingestion of a specific food. Testing is most commonly performed with a skin-prick test on the forearm. A positive test results when a raised red skin flare from histamine or other mediator release occurs within minutes as a reaction to the test substance. Alternately, allergen-specific IgE levels can be determined from serum samples that are tested with common food and environmental trigger antigens. Food allergies may be documented with a confirmatory oral food challenge. These challenges should be performed in a controlled environment with resuscitation equipment if anaphylaxis or a severe reaction to the food is suspected.

Allergic contact dermatitis is a differential diagnosis to AD, but both conditions can coexist. These two conditions can be challenging for physicians to distinguish. Patch testing that can detect delayed hypersensitivity (48 and 72 hours) to common allergens (eg, nickel, cobalt, neomycin, and so on) should be performed with a history or examination suggestive of allergic contact dermatitis. The patches are applied to the back of patients with suspected contact allergies. The patches are then removed at 48 hours, the sites marked, and a final reading for allergic sensitivity should be made at 72 hours.

FIRST-LINE THERAPIES

Interventional Education

Patient education about their skin condition is a crucial component of providing effective healthcare delivery. The treatment of AD can be exceedingly demanding, resulting in poor adherence to therapy. Educational programs including nurse-led eczema workshops can reduce AD severity and improve the quality of life of pediatric AD patients when compared with standard of care.[20,21] Often, AD is more effectively managed through an interprofessional team of AD specialists (dermatologist or allergist, nurses, psychologists, and dietitians) to address the patients' medical management, psychological, and behavioral factors.[22]

Consider how information will be delivered to the patient. Video-based educational formats have improved patient AD education when compared with a written pamphlet.[23] Support groups have also reported significant psychosocial improvements to AD-related pruritus symptoms, mood, and quality of life.[24] There are four prominent organizations in North America from which patients can obtain further AD information: The National Eczema Association (www.nationaleczema.org), American Academy of Dermatology (www.aad.org), Eczema Society of Canada (www.eczemahelp.ca), and the Canadian Skin Alliance (www.canadianskin.ca).

Topical Moisturizers and Bathing

The most important therapy patients with AD of all severity levels should consider is the use of moisturizers. The continued use of moisturizers for cutaneous hydration will abate associated xerosis and pruritus and reduce the number of flare-ups and the necessity of topical steroid preparations.[25,26] Moreover, there is some evidence that the habitual use of moisturizers from birth is an efficacious approach to prevent AD in infants considered to be high risk.[27]

Moisturizing has several key roles in treating the skin, including assisting in repair of the damaged skin barrier, lessening transepidermal water loss, maintaining skin hydration, alleviating dry skin, and reducing the need for topical corticosteroids (TCSs).[28] The stratum corneum's primary function is to prevent transcutaneous evaporation of water.[28] A minimum of 10% moisture content is necessary for the stratum corneum to function.

Moisturizer choice is based on factors such as the site of application, season, patient preference, and degree of dryness of the skin. Moisturizers can be formulated in a variety of delivery systems including creams, ointments, lotions, and gels. Creams are an emulsion of continuous water with suspended oil that are often well tolerated and not greasy. Ointments have the highest moisturizing ability of all the formulations because of a very high lipid composition (continuous oil phase with a potential suspended water component). Ointments are more occlusive and tend to cause less stinging than gels (powder suspended in a lattice), but patients may find ointments uncomfortable, itchy, or sticky. Gels facilitate transport down hair follicles and may be drying. Lotions (powder in water) contain a higher percentage of water relative to oil, and because they evaporate, they tend to be used on areas where drying effects are not as troublesome (eg, the scalp and chin).

No study to date has demonstrated one moisturizer preparation to be superior to another. Topical preparations with known allergens including perfumes and lanolin should be avoided. There are three classes of moisturizers patients with AD can be treated with. Refer to Table 4 for a classification of moisturizers (humectant, emollient, occlusive types), along with their properties.

Patients should not overbathe. One suggestion is to take warm water baths or showers for no more than 5 to 10 minutes. The water may prepare the skin for more permanent hydration treatments of the stratum corneum and helps to eliminate scales, crust, sweat, irritants, and allergens.[29] Patients should avoid taking bubble baths or bathing with scented oils and fragrances.

Table 4.
MOISTURIZERS

Class	Mode of Action	Adverse Reactions	Examples
Humectants	A moisturizer that contains an ingredient that attracts water molecules out from the environment and toward itself. This helps rehydrate the skin's surface.	Irritation – urea, lactic acid (apply to intact damp skin)	Glycerin, propylene glycol, urea, lactic acid, hyaluronic acid
Emollients	A moisturizer that contains an ingredient that is composed of lipids and lubricates the skin by filling the cracks between desquamating corneocytes.	Rare contact irritant dermatitis	Cholesterol, squalene fatty-acids, alcohols, "pseudo-ceramides"
Occlusives	A moisturizer that contains ingredients that form a protective hydrophobic film over the skin and prevents transcutaneous water loss.	Messy, folliculitis (mineral oil), acneiform, contact allergy (lanolin)	Petroleum, beeswax, mineral oil, zinc oxide

Whereas taking warm water baths in conjunction with non-irritating, mild acid soaps is encouraged, scrubbing the skin is highly discouraged and should be avoided. Moisturizers should be introduced within 3 minutes after exiting the shower or lukewarm bath because the skin can become very dry without it.[30]

It is imperative that patients become educated on proper use of moisturizers to improve skin function and appearance. Refer to Table 5 for evidence of interventional education and moisturizing in improving outcomes in patients with AD. The study by Chiang and Eichenfield[33] documented the best results when moisturizers were used without routine bathing.

Topical Corticosteroids

Topical corticosteroids are used as a first-line prescription therapy for both adults and children to treat inflammatory symptoms and signs of AD including acute flares and itchiness. Thei use is well validated, with more than 100 randomized controlled trials performed[35] demonstrating that they reduce the acute and chronic signs of AD.[37]

The most preferable TCSs are those that are formulated with low systemic bioavailability and a favorable therapeutic index matched to the area of the involved skin (Table 6) particularly for infants and young children with widespread involvement.[37,38] When selecting the potency of the TCS, be cognizant of the patient's age, disease severity, and thickness of the involved skin region/relative absorption (Table 7).

Potential adverse risks associated with TCSs include skin atrophy, perioral dermatitis, adrenal suppression, acne rosacea, and the development of striae. After the lesion appears to have resolved, patients should taper their use to every other day before beginning maintenance therapy. Long-term use of medium-potency TCSs with proactive twice-weekly application in conjunction with emollient use can reduce the risk of relapse for adults and children with moderate to severe forms of AD.[39–41]

High-potency TCSs (more than three times 1% hydrocortisone) should not be routinely used on thin skin such as the face, body folds, and groin because of the risk of cutaneous atrophy. The appropriate amount of cream or ointment that should be dispensed often for 2 weeks of use is measured in adult fingertip units, or approximately 0.5 g applied over an area

Table 5.
EVIDENCE FOR MOISTURIZING IN PATIENTS WITH ATOPIC DERMATITIS (AD)

Study	Results
6 week randomized controlled trial; education of parents improved AD in children, adolescents[31]	12-month improved quality-of-life scores Decreased severity of eczema
Emollients improve treatment results with topical corticosteroids in childhood AD: randomized comparative study[32]	52 patients aged 2–12 y Significantly improved pruritus and xerosis
Qualitative assessment of combination bathing and moisturizing on skin hydration AD[33]	Bathing and no moisturizing may compromise hydration Bathing and moisturizing provides modest hydration Applying moisturizer alone provides greatest benefit
A pilot study of emollient therapy for the primary prevention of AD[34]	22 neonates at high risk admitted to study 20 evaluable and 3 patients (15%) developed AD Less than historic controls because of a protective emollient effect

Table 6.
CLASSIFICATION OF TOPICAL CORTICOSTEROIDS[34]

Estimated Relative Potency	Region of Use	Examples
X1 – Very low	Face, folds	Hydrocortisone 1%
X3 – Low	Resistant, kids	Desonide 0.05%
		Hydrocortisone 17 valerate 0.2%
		Betamethasone valerate 0.05%
X6 – Moderate	Hands/feet	Betamethasone valerate 0.1%
		Mometasone furoate 0.1%
X9 – High	Palms/soles	Fluocinonide 0.05%
X12 – Ultrahigh	Resistant palms/soles	Clobetasol propionate 0.05%

the size of two adult palms. Clinicians often underestimate or overestimate the quantity of topical steroids to order. Table 8 provides a guide to appropriate quantities depending on the extent of involvement in each area.[42]

Topical Calcineurin Inhibitors

There are two nonsteroidal topical calcineurin inhibitors (TCIs): tacrolimus and pimecrolimus. Tacrolimus 0.1% is approved for adults only. Although tacrolimus 0.03% ointment and pimecrolimus 1% cream are officially indicated only for patients with AD older than 2 years, the recent American Academy of Dermatology guidelines recommend their off-label use in patients younger than 2 years with mild or severe disease.[29] The major adverse reactions to TCI use are transient, local burning or itching sensations at the site of application (keeping the topical cream/ointment in the refrigerator may partly alleviate this). That said, long-term use of TCIs is not associated with skin atrophy, and they can preserve the epidermal barrier further weakened by topical steroid application.[43] One study illustrated that tacrolimus ointment 0.1% has shown efficacy and safety for long-term treatment of up to 12 months in children with AD.[44] Similarly, one open-label clinical study reported that tacrolimus 0.1% has been shown to be safe and effective in adult patients with AD.[45] Moreover, a 6-month controlled clinical trial observed that 1% pimecrolimus cream was well tolerated and effective in patients (infants and adults) with AD.[46]

Occasionally, patients may develop an allergy to these agents, and the cost may be a deterrent for individuals who do not have coverage for these topical agents. There is a black box warning about the use of these agents and the theoretical risk of lymphoma, which was based on lymphomas noticed in mice exposed to extreme doses of the drug.[47] However, there does not appear to be any increased risk of this cancer in humans using TCIs.[47]

Tacrolimus ointment 0.1% is indicated for moderate to severe AD, often used in combination with TCSs, while pimecrolimus cream 1% is indicated for mild to moderate AD. Topical calcineurin inhibitors are particularly recommended for the treatment of AD that manifests on the eyelid, facial regions, and intertriginous areas. Moreover, they are suitable in patients with frequent flares or persistent AD who otherwise would require the prolonged use of TCSs. Even though there are concerns of the development of malignancies with chronic use of TCIs, there is currently no short- or medium-term (<10 years) evidence of increased risk of lymphoma in patients who used TCIs for a long period relative to the general population.[48,49] Recent studies have reported that patients using tacrolimus three times weekly for maintenance therapy experience greater flare prevention and longer times until first disease relapse.[50]

Preventive Therapy

Because AD is a chronic, relapsing inflammatory disease, it is now recommended that patients follow a long-term maintenance therapy rather than following the traditional "reactive" approach to flare-ups (Table 9). The preventive approach recognizes that previously involved lesional skin is far from normal. In actuality, the skin of AD patients has subclinical signs of inflammation, epidermal barrier defects, and damage. Always recommend the daily application of emollients or moisturizers to unaffected areas. They should be applied in the following scenarios: after bathing

Table 7.
TOPICAL STEROID PERCUTANEOUS RELATIVE ABSORPTION[37]

Region	Relative Absorption
Forearm	1.00
Plantar	0.14
Palm	0.83
Back	1.70
Scalp	3.70
Forehead	6.00
Cheeks	13.00
Scrotum	42.00

Table 8.
QUANTITY OF TOPICAL CORTICOSTEROID TO APPLY BY ANATOMICAL REGION[42]

	Quantity of medication (g)	
Region	**Males**	**Females**
Trunk (including buttocks)	6.6	5.8
One leg (groin to ankle)	2.9	2.5
One foot	0.9	0.7
One arm and forearm	1.7	1.3
One hand	0.6	0.5
Face, neck, and ears	1.3	0.9
Whole body	20	17

while the skin is still damp, after handwashing, anytime the skin is dry, and in the chronic stage to prevent recurrences of flares.

Comprehensive treatment and preventive therapy consist of three components.[51]

- Intensive TCSs twice daily for moderate to severe AD severity until remission flares and lesions have mostly cleared often in a week or slightly longer.
- Subacute eczema often has the appropriate TCS cream in the morning and TCI at night.
- Long-term low-dose intermittent application of TCI twice a week.

SECOND-LINE THERAPIES

Antimicrobial Therapy

Patients with bacterial infection should use topical and/or oral antibiotic therapy but should generally be restricted to short-term use in order to prevent the development of antibacterial resistance. Some evidence points to the use of first-generation cephalosporins for the treatment of *S aureus* that colonizes and causes superinfection in patients with AD.[52] Other clinicians will order antibiotics with effects against staphylococcus that also have anti-inflammatory action (eg, doxycycline, cotrimoxazole).

Bleach (sodium hypochlorite) baths may also be recommended as an adjuvant therapy in patients with AD and frequent or extensive secondary bacterial infections. It is suggested that the antiseptic effects of bleach can reduce the colonization of the skin by *S aureus*.[52] Patients should soak for 5 to 10 minutes in a bathtub full of lukewarm water mixed with one-quarter to one-half cup of 6% bleach solution.

Eczema herpeticum is characterized by numerous painful, monomorphic, "punched-out" lesions with hemorrhagic crusting. Patients with facial lesions should be referred to ophthalmology for assessment of possible retinal involvement. Cutaneous lesions should be swabbed for polymerase chain reaction identification of herpes simplex virus or varicella zoster virus. If results cannot be obtained within hours of testing if the morphology of lesions is consistent with herpes simplex virus, empiric treatment should be started. Treatment includes the antivirals acyclovir or its derivatives famciclovir and valacyclovir. Oral formulations are indicated for patients with a primary infection or severe involvement, including fever, malaise, and lymphadenopathy. Intravenous acyclovir is usually reserved for patients who cannot eat or drink, are immunocompromised, or have ocular or systemic involvement.

Patients with a dermatophyte (fungal) infection from *M furfur* (microscopic examination of involved skin scraping of the scale is best) should be treated with topical or systemic antifungal therapy (eg, topical "azole" agents). Some evidence suggests that the onset of AD can be delayed or prevented by 20% in the first 3 years of life when mothers are supplemented during pregnancy or during the infancy stage with probiotics.[53,54] One recent meta-analysis of the role of probiotics in AD occurrence indicated that both *Lactobacillus* alone and *Lactobacillus* with *Bifidobacterium* are protective against AD.[55]

Antihistamine Therapy

Scratching will induce histamine and other mediator release, thereby exacerbating the pruritus. This can become frustrating because patients may have difficulty sleeping. Both sedating and nonsedating oral antihistamines are often prescribed, with the nonsedating antihistamines less useful in managing AD for control of the pruritus. Sedating oral antihistamines (eg, hydroxyzine, diphenhydramine, doxepin) have been shown to improve patient sleep quality.[56] However, there is currently no evidence to suggest that antihistamines mitigate the AD progress.

Table 9.
OPTIMAL TREATMENT BY ECZEMA STAGE[51]

Eczema Stage	Topical Therapy	Frequent Moisturizer Use
Acute	Topical corticosteroid AM/PM	
Subacute	Topical corticosteroid AM Calcineurin inhibitor PM	• After bathing, while damp
Chronic	Calcineurin inhibitor twice per week to prevent recurrences	• After handwashing • When skin is dry • In the chronic stage to prevent recurrences • Any time the skin is dry

Avoidance of IgE-Mediated Triggers

There are myriad environmental and psychological factors that can aggravate and/or trigger AD. Patients should avoid common skin irritants including harsh antibacterial soaps, detergents, fabric softeners, chemicals, wool or nylon clothing, abnormal temperature/humidity, or sudden changes in temperature.[57] Cotton or corduroy clothes are often most comfortable next to the skin surface. Encourage patients to double rinse their clothing with white vinegar to remove detergent residue in the clothes. Launder new clothing before use and maintain a pleasant temperature and humidity level in the patient's environment.

Up to one-third of AD patients are known to have an IgE-mediated food allergy.[58] The most common implicated foods include milk, egg, peanut, wheat, and soy. Indications for evaluation of possible food allergies in children younger than 5 years include (1) persistent AD despite optimized treatment or (2) having a reliable history of immediate reaction after ingestion of a specific food.[59] In children, eliminating foods from the diet can cause potential growth deficiencies, and it is critical to consume a balanced diet for proper growth.[58] Moreover, children can outgrow nutrition-associated AD and/or become tolerant to certain foods, and so allergenic foods may be reintroduced every 6 to 12 months to see if the allergy has resolved with induced tolerance.[58]

Positivity to aeroallergens tends to increase with age. Dust mites in particular are the most common allergen in patients with AD, and avoiding them has been helpful to patients.[60,61] Dust mites live in pillows, mattresses, and carpets. It is recommended that patients wash their bedding weekly in hot water; encase pillows and mattresses; vacuum frequently;[57,63] and minimize use of carpeting, curtains, and drapes to control or mitigate AD.

Oral Phosphodiesterase Inhibitors

Elevated levels of phosphodiesterase type 4 (PDE4) are associated with increased production of proinflammatory cytokines

Table 10.
THIRD-LINE SYSTEMIC/BIOLOGIC THERAPIES AND PHOTOTHERAPY FOR SEVERE AD

Therapy	Comments
Oral cyclosporine A (CSA)[64]	Dosed at 2.5–5 mg/kg per day or alternatively or 3 mg/kg per day in children, or 150 mg (low dose) or 300 mg (high dose) in adults
	Response seen in 2–3 wk
	Risks with long-term therapy: hypertension, renal toxicity, malignancy
	Therapy beyond 1 y is not recommended
	Monitor blood pressure and serum creatinine bimonthly for the first 3 mo and less frequent afterward
Azathioprine (AZA)[65–67]	AZA metabolism depends on thiopurine methyltransferase (TPMT) activity levels
	Perform genotype or baseline TPMT activity testing prior to AZA therapy
	Dosed at 2.5 mg/kg per day in patients with normal TPMT levels and 1.0 mg/kg per day for patients with lower TPMT level
Mycophenolate mofetil (MMF)[68,69]	Dosed at 40–50 mg/kg per day in younger children and 30–40 mg/kg per day in adolescents
	Maximal effect after 8–12 wk of therapy
	Monitor for leukopenia and anemia
	Reduce doses with renal failure
Methotrexate (MTX)[70,71]	Less immunosuppressive, more anti-inflammatory
	Response plateau at 12 wk/15 mg per wk
	Concerns of nausea, liver function abnormalities/hepatotoxicity, pulmonary toxicity — limit dosing
Dupilumab (biologic, expensive)[72,73]	Human monoclonal antibody α subunit IL-4 receptors—blocks IL-4, IL-13
	Improved inflammation, pruritus
	Often criteria for use — failure topical/systemic agents/not covered by all insurers
Phototherapy (not available in all centers, infrequent use)[74–77]	For patients whose condition is not controlled with topical therapy
	UVA (340–400) acute severe AD flares, NB-UVB (311 nm) chronic form of AD
	Adverse effects include sunburn, increased redness, sweating, pruritus, pain, and pigmentation.
	Cutaneous malignancies, photosensitivity (preexisting or induced by treatment)

and chemokines, which elicit flares in AD. Apremilast is an oral PDE4 inhibitor with promising efficacy and safety. In phase II trials, adult patients with moderate to severe AD have had mean reductions of 19% to 39% in the Eczema Area and Severity Index after a treatment regimen of 20 mg of apremilast twice daily for 3 months or 30 mg twice daily for 6 months.[63]

THIRD-LINE THERAPIES

Systemic Anti-inflammatory Therapies

When patients fail to see any improvement from first- and second-line therapies, systemic anti-inflammatory treatments may be required.[64] The oral anti-inflammatory agents listed in Table 10 are all immunosuppressive and are generally restricted for those with severe, frequent flares and/or those patients who are using hazardous levels of topical therapies. Patients should be carefully assessed before prescribing anti-inflammatory agents and closely monitored for potential adverse reactions, and treatment should be limited to a short duration.

Phototherapy

Phototherapy is a therapeutic option for those patients whose AD cannot be controlled with topical medications alone and/or who have extensive body spread.[74] Phototherapy can work in tandem with TCSs to treat AD. Incorporating the use of both oral and topical psoralen with UV light therapy has been shown to reduce symptoms of pruritus within the first 2 weeks of treatment.[76]

NEW AND PROMISING AGENTS

Crisaborole

One novel technique used to treat AD is the boron-based benzoxaborole compound crisaborole, available as a 2% topical ointment. Crisaborole is a nonsteroidal, anti-inflammatory medication that is capable of selectively targeting PDE4.[78,79] By inhibiting PDE4, crisaborole effectively up-regulates concentrations of intracellular cyclic adenosine monophosphate, which is also a regulator of nuclear factor κ light-chain enhancer of activated B cells and nuclear factor of activated T-cell signaling pathways.[80] This results in the suppression of various proinflammatory cytokines, thereby controlling inflammation.[81,82] Data from two large randomized controlled phase 3 clinical trials demonstrated that crisaborole topical ointment 2% could be used safely and efficaciously in children, adolescents, and adults with mild to moderate AD.[83,84]

Dupilumab

The most promising biologic for AD is dupilumab. It is a human monoclonal antibody directed at the α subunit of IL-4 receptors. Inhibiting the α subunit blocks IL-4 and IL-13 signaling and effectively reduces the TH2 response. Dupilumab has caused significant improvement in inflammation and pruritus with no dose-limiting toxicity.[72] Advantages include lack of immunosuppressive effects or need for bloodwork monitoring. The most common adverse reactions include injection site reactions and conjunctivitis (10% each). It is used for the treatment of adults with moderate to severe AD who have failed current topical and systemic treatment options.[73] The treatment is expensive and not covered by all insurance providers.

CONCLUSIONS

The future of AD management begins with identifying the at-risk baby at birth. Conceptual models of hydrating the skin from the first few days of life and topically seeding protective skin bacteria are all intriguing hypotheses that may prevent or modify the atopic march. The recognition of the genes responsible for defective barrier function is key to immune modulation and the development of newer classes of therapies, including Janus kinase signaling pathway inhibitors, additional PDE4 inhibitors, and agonists of the aryl hydrocarbon receptor. Above all, new drugs are useful only in concert with patient-centered care, a patient support network, and interprofessional healthcare teams. Innovative solutions can lead to improved AD prevention and management.

PRACTICE PEARLS

- Atopic dermatitis is a chronic, relapsing, intensely itchy inflammatory skin disease with characteristic infantile, childhood, and adult clinical stages.
- Triggers for AD include increased susceptibility to microbial colonization and infection, dust mite sensitivity, and environmental/psychosocial factors.
- The primary concern in AD is barrier function and treatment; humectant or lubricating moisturizers are key to disease control along with appropriate antihistamines to control pruritus.
- Atopic dermatitis often requires topical steroid treatment with subacute stages responding to TCSs combined with TCIs that can also delay or prevent recurrences with twice-weekly applications.
- Resistant cases may require investigation into IgE levels and secondary bacteria management and the use of systemic immunosuppressive or biologic agents.

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