Original article

Atopic Dermatitis: clinical aspects and treatments

ABSTRACT

Atopic Dermatitis is the most common eczematous inflammatory skin condition, presenting with lesions that typically appear as poorly demarcated erythematous and scaly papules and plaques. The lesions most commonly occur on flexural surfaces of the knees, elbows, and wrists and are associated with moderate to severe itching. This article focuses on the clinical presentation of atopic dermatitis and treatment options. Other related topics include epidemiology, pathogenesis, risk factors, triggers, and differential diagnoses.

Keywords anti-inflammatory therapies, atopic dermatitis, biologics, eczema, lesions, phototherapy, risk factors, trials

For referencing Geng RSQ, Sibbald RG. Atopic Dermatitis: clinical aspects and treatments. WCET® Journal 2024;44(2):29-36

DOI https://doi.org/10.33235/wcet.44.2.29-36

INTRODUCTION

Atopic dermatitis (AD), or atopic eczema, is the most common eczematous inflammatory skin condition, with a lifetime prevalence of 15%.[1] Although patients of all ages can be affected, onset peaks in infancy, with 90% of cases occurring before 5 years of age.[2] Notably, the prevalence of AD has increased two- to threefold over the past 3 decades.[3]

The pathogenesis of AD is multifactorial and involves a complex interplay between the skin barrier, genetic factors, and environmental exposures. Skin barrier dysfunction can be characterised by increased transepidermal water loss, increased skin pH, or decreased levels of ceramides, humectants, and structural proteins. Other challenges to skin barrier function include aberrant filaggrin (FLG; a protein that binds keratin fibers in epidermis) expression or excess soap usage, which can also increase skin permeability.[4] As mast cells and basophils become sensitised to environmental antigens, type I immunoglobulin E-mediated hypersensitivity reaction, cytokine release, and inflammation are triggered, often resulting in intense itching. Scratching of the lesions results in further damage to the skin barrier, referred to as the itch-scratch cycle. Chronically, this can lead to worsening inflammation and lichenification.[5]

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With the physical discomfort and cosmetic appearance of AD lesions, patients can experience significant psychosocial challenges, including social distress, embarrassment, and activity limitation.[6] Given the potential impact on quality of life and increasing incidence, this review will focus on the clinical features of AD and available treatment options.

RISK FACTORS

Atopic dermatitis is part of the atopic triad consisting of AD, asthma, and allergic rhinitis. There are several risk factors for developing AD, with the strongest predictor being a positive family history for any atopic disease, especially AD. The implicated genes include FLG, T_H2 cytokine cluster, and LRRC32 (which encodes glycoprotein A repetitions predominant).[7]

Environmental risk factors have also been identified: Living in an urban environment, dry climate, low UV light exposure, and a diet high in simple carbohydrates and polyunsaturated fatty acids are all associated with increased risk of AD.[7] Table 1 summarises risk factors associated with AD.

CLINICAL CLASSIFICATIONS

Although the clinical presentation of AD is heterogeneous with various features and symptoms, lesions are typically characterised as poorly demarcated, scaly, and erythematous papules that coalesce into plaques with severe itching that are most commonly found on flexural surfaces of knees, elbows, and wrists. The clinical features of AD are outlined in Table 2, with the essential, major, and minor features being indicated based on American Academy of Dermatology guidelines.[2] Because of the wide variation in clinical presentation of AD, there is a broad differential, outlined in Table 3. Classification of AD is based on biomarker serology (IgE), acuity of presentation, and age at onset. Clinical presentations of AD are provided in Figure 1.

Classification by Serum IgE Levels

Extrinsic. The extrinsic subtype is characterised by elevated total IgE levels (>200 kU/L) in response to specific protein allergens, typically from the *Dermatophagoides* genus of mites, including *Dermatophagoides pteronyssinus* and *Dermatophagoides farina*. The main elevated cytokines include interleukin 4 (IL-4), IL-5, and IL-13, characteristic of a T_H2 response. The extrinsic subtype arises from impaired skin barrier function, with 20% to 30% of patients having pathogenic FLG variants, and is much more common than the intrinsic subtype.[9]

Table 1 Factors associated with increased risk of developing Atopic Dermatitis.

Risk Factor Category	Description
Genetic	Family history - Atopic dermatitis - Asthma - Allergic rhinitis Genes - FLG - LRRC32 - TH2 cytokine cluster
Environmental	Diet (high simple carbohydrates and polyunsaturated fatty acids) Dry climate High household education level Low ultraviolet exposure Repeated antibiotics exposure before 5 years of age Small family size Urban environment

Intrinsic. The intrinsic subtype is characterised by normal total IgE levels (<200 kU/L) and shows a sexual predilection toward women. The main elevated cytokine is interferon γ, characteristic of a T_H1 response. Although the skin barrier is intact in the intrinsic subtype, metals and haptens can still penetrate the skin and trigger a response.[9]

Classification by Acuity of Presentation

Individual lesions of AD can be classified based on the acuity of presentation into acute, subacute, or chronic categories. An individual with AD may present with a combination of lesions in any of these different stages.

Acute. Acute lesions appear as poorly demarcated erythematous papulovesicular papules and plaque eruptions with blistering, weeping, and/or crusting. Widespread edema may also be present, with or without scales. Scratching can lead to erosions and pustules that are susceptible to secondary infection, primarily with *Staphylococcus aureus*.[10]

Subacute. Subacute lesions appear as poorly demarcated erythematous scaly plaques and papules.[10]

Chronic. Chronic lesions can involve lichenification (thickening of skin with increased visibility of skin markings) due to repeated scratching over time and scale.[10]

Classification by Age at Onset

Infantile (2 weeks to 2 years of age). Infantile-onset AD typically presents with lesions characterised as itchy papules and vesicles with associated serous exudate and/or crusting, most commonly affecting the head and neck. Lesions usually first appear as erythema and scaling on the cheeks, which then

Figure 1 Clinical presentations of Atopic Dermatitis
A, Poorly demarcated erythematous plaques with fine scale on flexural aspect of the elbow. B, Well-demarcated erythematous plaques distributed on the dorsal aspect of the feet, ankle, and below the knee. C, Poorly demarcated erythematous patch on the flexural aspect of the wrist.

Table 2 Features and symptoms of AD.

Features and Symptoms	Description
Essential features[a]	
Eczema	- A general term for describing skin that has a rash-like appearance, itchy or inflamed - Age-specific distribution: Children: facial, neck, extensor Adult: flexor - Sparing of groin and axilla
Pruritus	- Severe itchy sensation - Scratching or rubbing can further aggravate AD, leading to thickening over time and increases risk of secondary infection
Major features[b]	
Atopy	- Personal or family history of atopic diseases including AD, asthma, and allergic rhinitis - Increased immunoglobulin E reactivity
Early age at onset	- Most common between 3 and 6 months of age - 90% of cases occur before the age of 5 years
Xerosis	- Dryness in areas without apparent inflammation, usually in low-humidity environments - Often affects the legs but can be generalised
Minor features[c]	
Anterior neck folds	Horizontal folds midanterior neck
Dennie-Morgan folds	Symmetrical dark dual horizontal folds below lower eyelids
Follicular prominence	Goose-bump appearance of follicles
Hertoghe sign	Loss of lateral third of eyebrows due to repeated scratching
Ichthyosis vulgaris	Usually dry and thick scales. Can also be thin white-brown scales on the shins. Typically manifesting as a result of null FLG mutations, inherited in an autosomal semidominant pattern
Keratosis pilaris	Thick scale with variable erythema around hair follicles. Onset typically in childhood and frequently affects anterior thighs, extensor arms, and lateral cheeks
Palmar/plantar hyperlinearity	Exaggerated creases, more often in palms than soles; associated with null FLG mutations
Periorbital hyperpigmentation	Gray-violet-brown pigmentation of skin around eyes due to repeated edema and rubbing
Pityriasis alba	Poorly demarcated hypopigmented patches with fine scaling usually on the face and neck. Most commonly in children and younger adults
White dermatographism	Blanching response to stroking of the skin with back of fingernail due to excess capillary vasoconstriction and local edema. Often without wheals

Abbreviations: AD, Atopic Dermatitis; FLG, filaggrin.

[a]Essential features are those that must be present for a diagnosis of AD to be made.

[b]Major features are those that are observed in most cases and can support a diagnosis of AD.

[c]Minor features are less commonly observed, but can help suggest a diagnosis of AD.

Adapted with permission from Maliyar et al (2018).[8]

extend to the forehead, scalp, and neck. Extensor surfaces are also often involved as a result of trauma from crawling. Over time, scratching and rubbing can result in crusting and lichenification (thickening and increased skin surface markings).[8]

Childhood (2 years of age through puberty). In childhood-onset AD, facial involvement is less prominent, and instead the feet, ankles, wrists, and the flexural aspect of the knees and elbows are more commonly involved. Lesions are typically dry with lichenified plaques, papules, erosions (breakdown of epidermis with epidermal base), and/or crusts.[8]

Adult (postpuberty). Similar to childhood-onset AD, adult-onset AD primarily involves flexural regions, but also more commonly affects the face and neck. Lesions typically present as symmetrical, dry, scaly plaques, and papules. Excoriations and lichenification are commonly observed, whereas crusting and exudation are less frequent.[8]

SEVERITY SCORING

Once a diagnosis of AD has been achieved, describing the severity of the disease can guide treatment selection. The most commonly used severity scoring tools are the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD). Although both tools include the extent of erythema, swelling, excoriation, lichenification, and body area affected, the SCORAD also considers subjective patient measures.[11] A summary of the severity grading strata for EASI and SCORAD is provided in Table 4.

AD TREATMENTS

Several treatment options are available for treating AD lesions to provide symptomatic relief for patients and break the itch-scratch cycle to prevent disease progression and development of secondary infection. Counsel patients to regularly use moisturisers with emollients, humectants, and occlusive agents to improve the skin barrier, provide some itch relief, and prevent future flares.[12] Patients with AD should avoid products with fragrances to minimise potential exposure to allergens. Discuss the importance of identifying and avoiding factors that trigger or exacerbate AD lesions.[13] A list of common trigger factors is provided in Table 5, and a summary of treatment options for AD is provided in Table 6.

Pharmaceutical Topical Treatments

Topical moisturisers. Regular usage of moisturisers is the cornerstone of AD therapy. Moisturisers can contain a combination of humectants, occlusives, and emollients that help protect the skin barrier. Humectants are hydrophilic substances that hold onto water, occlusives are hydrophobic substances that form a physical layer over the skin to trap water below, and emollients fill spaces between dead skin cells to soften the skin.

In addition to helping patients manage dryness and itchiness of active AD lesions, moisturisers can also prolong relapse. In a trial involving 44 patients with AD lesions cleared by betamethasone 0.1% cream, those who applied an urea-containing moisturising cream as the sole maintenance therapy relapsed after more than 180 days on average, compared with 30 days for patients who did not use any maintenance therapy.[14]

Table 3 Differential diagnoses of Atopic Dermatitis and distinguishing features.

Differential Diagnoses	Distinguishing Features
Candidiasis	Skin lesions often accompanied by paronychia and thrush. Flexural erythema is accompanied by satellite papules or pustules.
Contact dermatitis	Lesion location and shape is dependent on the nature of the allergen or irritant exposure. Discrete well-demarcated margins with edema.
Impetigo	Erythematous lesions are well-demarcated and painful with honey-colored crusting.
Nummular dermatitis	Lesions are well-demarcated and most frequently present on extremities.
Psoriasis	Plaque lesions are well-demarcated, thick, more commonly appear on extensor surfaces and localized to areas of trauma (Koebner phenomenon). Nail pitting and joint involvement. Frequently involves diaper area in infants.
Scabies	Visible burrow patterns and palmoplantar pustules. Contagious.
Seborrheic dermatitis	Lesions usually pink patches with greasy white-yellow scale and are often hypopigmented. No excoriations. Infantile onset usually resolves before 2 years of age.
Tinea	Lesions are erythematous and well-demarcated with central clearing and advancing border.

Topical corticosteroids. Corticosteroids have anti-inflammatory properties that are used for treating acute flares and itchiness. In a trial involving 40 patients, those treated with mometasone furoate 0.1% cream nightly for 4 weeks achieved a 77% reduction in SCORAD score compared with 17% for Vaseline control ($P < .001$).[15] Corticosteroids are classified by their potency, and choice of corticosteroid should be guided by the patient's age, region of the body affected, and severity of disease. Generally, low-potency corticosteroids are used for milder disease, younger patients, and in areas involving the face and folds (intertriginous regions).[8] Long-term topical corticosteroid use is associated with further decreased skin-barrier function, skin atrophy, telangiectasia, and purpura and can induce or aggravate rosacea and perioral dermatitis. As such, corticosteroids are only recommended for short-term treatment of flares and symptom management. Intradermal corticosteroid injections can also be provided to provide fast-acting relief for acute flares.

Topical calcineurin inhibitors (tacrolimus and pimecrolimus). Tacrolimus and pimecrolimus are calcineurin inhibitors with anti-inflammatory properties and skin barrier-preserving properties used in treating AD. In one trial, 49 patients who applied tacrolimus 0.1% ointment twice daily for up to 22 days achieved 72% reduction in EASI score compared with 26% for vehicle ($P < .001$).[16] Unlike corticosteroids, long-term tacrolimus or pimecrolimus use is not associated with skin atrophy; they can be used to reduce corticosteroid load or for maintenance.[17] Patients may experience burning or stinging upon application, but cooling the product in the refrigerator prior to application can alleviate this sensation.

Topical phosphodiesterase-4 inhibitors (crisaborole). Crisaborole is a phosphodiesterase-4 inhibitor with efficacy in treating AD through downregulating the production of proinflammatory cytokines. In one study involving 400 patients, those treated with crisaborole 2% ointment twice daily for 4 weeks achieved a mean reduction of 60% in EASI score compared with 43% for vehicle ($P = .0002$).[18] Crisaborole is generally well tolerated and is another steroid-sparing option for treating AD.

Topical anti-infectious agents. Anti-infectious agents are typically used as adjunctive therapies in cases where there is accompanying infection or if it is believed that a microbial factor (eg, *S aureus*) is aggravating the AD.

Fusidic acid and mupirocin are antibiotics used for targeting staphylococcal and streptococcal bacteria and can be effective in treating AD if *S aureus* colonisation is a contributing pathogenesis factor. In one trial involving 239 patients, those treated with fusidic acid 2% plus hydrocortisone 1% cream showed significant improvements in factors including erythema, itching, and scaling compared with patients treated with fusidic acid 2% cream or hydrocortisone 1% cream alone ($P = .009$).[19]

Soaking with bleach (sodium hypochlorite) is another option for reducing colonisation by *S aureus*. Patients can mix a quarter to a half cup of 6% bleach solution with a bathtub full of water and soak for 5 to 10 minutes.

Table 4 EASI and SCORAD severity grading strata.

Severity	EASI Score	SCORAD Score
Clear	0	0-9.9
Mild	0.1-5.9	10-28.9
Moderate	6-22.9	29-48.9
Severe	23-72	49-103

Abbreviations: EASI, Eczema Area and Severity Index; SCORAD, SCORing Atopic Dermatitis.

Table 5 Triggers and exacerbating factors of Atopic Dermatitis.

Type	Examples
Airborne allergens	Animal dander, dust mites, mold, pollen
Allergic irritants	Hard water, solvents
Contact irritants	Fragrances, wool (lanolin)
Environmental	Climate changes (eg, drops in humidity, colder temperatures), prolonged exposure to heat
Food allergens	Egg, fish, milk, peanut, shellfish, soy, wheat
Microorganisms	Bacteria: Pseudomonas species, Staphylococcus aureus, Streptococci species Yeasts and fungi: Candida species, Malassezia species, Trichophyton species
Physiologic/psychological	Stress, sweat

Systemic Pharmaceutical Treatments

Corticosteroids. Although corticosteroids can be taken orally, this is often not recommended due to rebound flares on cessation and adverse effects associated with systemic corticosteroid use (eg, weight gain, diabetes, muscle loss, gastrointestinal bleeds, etc). However, systemic corticosteroids may have benefits for treating severe acute flares.[20]

Calcineurin inhibitors (cyclosporine). Cyclosporine is a calcineurin inhibitor with anti-inflammatory properties that is useful in treating severe or recalcitrant forms of AD that have failed to respond to topic therapy. In one trial involving 46 patients, those who were treated with cyclosporine 5 mg/kg per day for 6 weeks achieved a mean 55% improvement in total body severity assessment score; in contrast, those with placebo worsened by 4% ($P = .0002$).[21] Although cyclosporine offers rapid relief, its effects are not long-lasting, and maintenance therapy is required to prevent relapse.[22] Renal impairment is a concern for initiating cyclosporine treatment and must be carefully monitored.

Purine analogs (azathioprine). Azathioprine is a corticosteroid-sparing immunosuppressant used in several inflammatory skin diseases including AD. In a trial involving 37 patients, those treated with azathioprine 2.5 mg/kg per day for 12 weeks reported a mean 26% improvement on factors including erythema, dryness, and lichenification compared with 3% for placebo ($P < .01$).[23] Although azathioprine has similar indications for usage in treating AD as cyclosporine, it is less preferred for acute flares because it does not act as fast. Hepatotoxicity is a concern for initiating azathioprine treatment.

Table 6 Treatment options for Atopic Dermatitis.

Topical Therapies	Systemic Therapies
Corticosteroids[a]	Antihistamines[b]
Crisaborole	Azathioprine
Moisturizers[a]	Biologics
Anti-infectious agents[b]	Dupilumab
Fusidic acid	Tralokinumab
Mupirocin	Corticosteroids
Calcineurin inhibitors[b]	Cyclosporine
Pimecrolimus	Janus kinase inhibitors
Tacrolimus	Methotrexate
	Mycophenolate mofetil
	Phototherapy
	Broadband UV-B
	Narrowband UV-B

[a]First-line therapies.
[b]Second-line therapies.

Folic acid inhibitors (methotrexate). Methotrexate has immunosuppressive properties and can be used in low doses to suppress AD symptoms and flares in moderate to severe cases. In a study involving 40 patients, methotrexate was as effective as cyclosporine.[24] Patients treated with methotrexate 7.5 mg/wk achieved a mean reduction of 26 SCORAD points compared with a 25-point reduction for those treated with cyclosporine 2.5 mg/kg per day ($P = .93$).[24] Similar to azathioprine, hepatotoxicity should be considered.

Inosine monophosphate dehydrogenase inhibitors (mycophenolate mofetil). Mycophenolate mofetil is another immunosuppressant with efficacy in treating AD. In a pilot study, 10 patients treated with 2 g/d for 4 weeks followed by 1 g/d for 4 weeks achieved a 55% decrease in SCORAD score ($P < .01$).[25] Mycophenolate does not act as fast as corticosteroids or cyclosporine, but it can achieve satisfactory clinical control with fewer adverse effects and be used for maintenance therapy.

Biologics. Currently, the only approved biologics for treating AD are dupilumab and tralokinumab, both of which target the IL-13 signalling pathway. However, many other biologics are in development.

Dupilumab. Dupilumab is an IL-4/IL-13 inhibitor used in treating moderate to severe cases of AD that are recalcitrant to other topical and systemic therapies. In a trial with 671 patients, 38% of patients treated with dupilumab 300 mg subcutaneously every 2 weeks and 37% of those treated weekly for 16 weeks achieved clear or almost clear on the Investigator's Global Assessment scale compared with 10% for placebo ($P < .001$).[26] Dupilumab greatly improves inflammation and itchiness without dose-limiting toxicity but is an expensive treatment.

Tralokinumab. Tralokinumab is an IL-13 inhibitor with similar indications for use as dupilumab. In a trial with 802 patients, 25% of those treated with tralokinumab 300 mg subcutaneously every 2 weeks for 16 weeks achieved EASI 75 compared with 13% of patients in the control group ($P < .001$).[27] Whereas both tralokinumab and dupilumab are effective, tralokinumab is associated with a lower risk of conjunctivitis.

Janus kinase inhibitors. Janus kinase (JAK) inhibitors are small-molecule inhibitors that target the JAK signalling pathway, which is associated with several proinflammatory cytokines. In a trial involving 560 patients, 80% of those treated with upadacitinib 30 mg daily for 16 weeks achieved EASI 75 compared with 16% for placebo ($P < .0001$).[28] In addition to offering high-target specificity like the biologics, JAK inhibitors can be applied topically (tofacitinib, ruxolitinib, delgocitinib) or taken orally (tofacitinib, baricitinib, abrocitinib, upadacitinib), offering a simpler route of administration.

Currently, three JAK inhibitors have been approved by the US Food and Drug Administration for use in AD. The first was ruxolitinib, a JAK1/2 inhibitor that was approved in 2021. The newer JAK1 selective inhibitors, upadacitinib and abrocitinib, were approved in 2022. Because of the novelty of these agents, their safety information may not be comprehensive, and

clinicians should practice extra caution. Janus kinase inhibitors have black box warnings including increased risk of serious infection, malignancy, and lipid level changes. The US Food and Drug Administration added additional black box warnings for JAK inhibitors in 2022 because of an increased risk of adverse cardiovascular events, including heart attack, stroke, and blood clot formation. However, this finding was from a trial studying the incidence of major adverse cardiovascular events in patients over the age of 50 years with rheumatoid arthritis and at least one cardiovascular risk factor being treated with tofacitinib, with nearly 100% of patients taking methotrexate and more than 50% taking prednisone concurrently.[29] Although clinicians should always pay close attention to black box warnings, it should be noted that the patient demographics in that study are not representative of AD patients, nor does the treatment regimen represent one that would be used in patients with AD.

Antihistamines. Antihistamines are used as an adjunctive treatment in AD to provide itch relief but do not treat the underlying disease itself. Even so, histamines should be considered in patients experiencing great discomfort due to the itchiness, because breaking the itch-scratch cycle is key to preventing disease progression and complications. This is especially relevant for patients who experience difficulty sleeping, in which case sedating antihistamines can provide relief.[30]

For relieving itch at night, use first-generation antihistamines (eg, diphenhydramine, hydroxyzine, etc), which provide a sedative effect to aid in sleep. For daytime, it is best to use second-generation antihistamines (eg, cetirizine, bilastine, etc), which are much less sedating because of their diminished ability to cross the blood-brain barrier.

Phototherapy

Phototherapy is another option for patients whose AD cannot be controlled solely with topical therapy or who have extensive bodily involvement. Phototherapy modalities have shown efficacy in treating AD, including broadband UV-B and narrowband UV-B. Narrowband UV-B is considered first-line phototherapy, but its use can be limited by overheating and sweating, which can flare AD.[31]

CONCLUSIONS

Atopic dermatitis is the most common eczematic inflammatory skin condition, and it may reduce patients' quality of life because of physical discomfort (itching, sleep disturbances) and adverse cosmetic effects. Management of AD often involves a combination of targeting the underlying disease and symptom management to break the itch-scratch cycle to prevent further exacerbation and promote disease remission. This can be achieved through the regular use of moisturisers and avoidance of triggers combined with either topical or systemic therapies.

PRACTICE PEARLS

- Atopic dermatitis can be classified according to serum IgE levels, age at onset, and time of presentation.
- Atopic dermatitis lesions typically appear as poorly demarcated, scaly, and erythematous plaques associated with severe itching, most commonly found on flexural surfaces of knees, elbows, wrists, and sides of fingers.
- Use of moisturisers with emollient, humectant, or occlusive agents and avoidance of triggers are key to treatment.
- Symptomatic treatment to relieve physical discomfort and break the itch-scratch cycle can improve quality of life and prevent further exacerbation.
- Therapies with anti-inflammatory properties are the cornerstone of AD treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

The authors received no funding for this study.

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