

REVIEW ARTICLE

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Atopic Dermatitis

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ATOPIC DERMATITIS IS ONE OF THE MOST PREVALENT INFLAMMATORY skin diseases. It usually develops in childhood and may persist into adulthood; less frequently, it starts in midlife or late life. The disorder is characterized by recurrent, pruritic, localized eczema, often with seasonal fluctuations. Many patients also have allergic asthma, allergic rhinoconjunctivitis, food allergies, and other immediate hypersensitivity (type 1) allergies. The disease was described and termed atopic dermatitis in the 1930s, with “atopic” reflecting the Greek word *atopos* (“without place”) to indicate the frequent, concomitant occurrence of IgE-mediated hypersensitivity reactions such as asthma.¹ Atopic dermatitis remains the preferred term for the disorder, but several other labels have been used, including atopic eczema, neurodermatitis, atopiform dermatitis, and most commonly, eczema.

EPIDEMIOLOGIC FEATURES

The prevalence and incidence of atopic dermatitis have increased over the past several decades.^{2,3} The Global Burden of Disease study showed a prevalence of 15 to 20% among children and up to 10% among adults, making atopic dermatitis the 15th most common nonfatal disease and the skin disorder with the highest disease burden, in terms of disability-adjusted life-years.⁴ In a retrospective study, health care utilization and annual treatment costs were higher for patients with atopic dermatitis than for matched controls without atopic dermatitis and were associated with the severity of the disease.⁵ Both sexes are affected, and the prevalence varies among races and ethnic groups.^{6,7} For example, in the United States, the prevalence is higher among Black children (19.3%) than among White children (16.1%).⁸ The increasing prevalence in high-income and industrialized countries has been tentatively attributed to environmental factors such as exposure to air pollution and household hygiene products.

CLINICAL FEATURES

The clinical characteristics of atopic dermatitis vary depending on age, disease stage, race or ethnic group, and geographic location. Typical acute lesions in White patients and Black patients are circumscribed patches of eczema (Fig. 1A through 1D); erythema is more frequently violaceous or even invisible in Black patients. The lesions are characterized by papules, papulovesicles, edema, crusting, and scaling (Fig. 1E), with hyperpigmentation or hypopigmentation of lesions after healing. In severe atopic dermatitis, areas of eczema coalesce into larger regions of generalized redness of the skin (erythroderma) (Fig. 1F).

In children, eczema may be widespread on the body, involving the head, face, cheeks (Fig. 1A and 1B), and arms and legs, with frequent involvement of the



Figure 1. Clinical Presentations of Atopic Dermatitis.

Shown are acute eczema in a 14-month-old girl (Panel A), rarefaction of the lateral eyebrows (Hertoghe's sign) in a 12-year-old boy (Panel B), leg eczema with violaceous erythema in a child (Panel C), leg eczema in a 4-year-old patient (Panel D), dry skin (xerosis) (Panel E), erythroderma in an 85-year-old patient (Panel F), circumscribed and hyperpigmented lichenification overlying eczema in a 7-year-old patient (Panel G), and eczema herpeticum in a 17-year-old boy with atopic dermatitis (Panel H). Panels C and G are used with permission from VisualDx.

ventral wrists and trunk.⁹ In contrast to previous assumptions, the area of skin covered by a child's diaper is also frequently involved.⁹ With increasing age of the patient, lesions tend to be more circumscribed and confined to the arms and legs, mainly the popliteal flexures and the hands, lower legs and feet, neck, and periorcular region. The rates of hand and foot dermatitis are higher among adults than among children.⁹

The appearance of lesions also varies in relation to race or ethnic group and geographic region.⁹ Phenotypes that are more common in White, Black, or Asian patients have been proposed,⁹⁻¹¹ but these findings need to be confirmed. For example, lesions on the trunk are found in all races and ethnic groups but are most clearly demarcated and most common in Asians.⁹⁻¹¹

Pruritus is a hallmark of atopic dermatitis,⁹ and the intensity of the itching broadly corresponds to the severity of the disease.¹² Pruritus

is aggravated by stress, sweating from physical activity or environmental heat, and humidity, as well as from contact with woolen clothes.¹² Pruritus-related scratching induces excoriations, bleeding, or the formation of hemorrhagic crusts. Persistent scratching leads to lichenification (Fig. 1G), as well as prurigo nodularis, which is characterized by generalized, severely itchy nodules.

Patients with atopic dermatitis have a range of associated clinical signs, such as a rarefaction of the lateral eyebrows (Hertoghe's sign) (Fig. 1B) or increased density and depth of palmar creases (hyperlinear palms).⁹ In most patients (75%), areas of dry skin (xerosis) (Fig. 1E) occur, even during remission of eczema.⁹ The presence of these signs helps establish the diagnosis of atopic dermatitis, but their absence does not rule it out. Atopic dermatitis has a chronic, fluctuating course. However, the aforementioned clinical signs and chronic scratching-related lesions,

Clinical Features	Description
Essential features	
Eczema	Chronic or relapsing eczema with characteristic morphologic features and age-specific patterns
Stage	Acute, subacute, or chronic
Severity	Mild, moderate, or severe
Immunoendotype	Th2 cells in Whites and in Blacks, Th2 and Th17 cells in Asians
Pruritus	
Important features	
Early age at onset	Typically between 2 mo and 6 mo of age
Atopy	Personal or family history or both, IgE reactivity (elevated total or allergen-specific serum IgE or both, seen in up to 80% of patients) †
Xerosis	
Associated features	
Atypical vascular responses	Facial pallor or white dermographism, for example
Perifollicular lesions	Keratosis pilaris, perifollicular accentuation
Ocular or periorbital changes	Hertoghe's sign
Other regional findings	Perioral changes, periauricular lesions, pityriasis alba, hyperlinear palms, ichthyosis
Scratching-related chronic lesions	Lichenification, prurigo lesions
Related conditions	Bacterial skin infections (impetigo, skin abscesses), viral skin infections (eczema herpeticum, molluscum contagiosum infection), fungal skin infections (dermatophytosis, candidiasis), allergic disorders (asthma, rhinitis, rhinoconjunctivitis, food allergy), inflammatory bowel disease, rheumatoid arthritis, cardiovascular disease (debated), quality-of-life impairment (sleep disturbance), anxiety, depression, suicidality

* The information presented is modified from Eichenfield et al.¹⁵ Essential features are those required for the diagnosis of atopic dermatitis. Important features are those observed in most cases, adding support to the diagnosis. Associated features suggest the diagnosis but are too nonspecific to be used in defining or detecting atopic dermatitis for clinical and epidemiologic studies. Th2 denotes type 2 helper T cell, and Th17 type 17 helper T cell.

† Monitoring of IgE levels is not recommended for the routine assessment of disease severity.

such as lichenifications, persist during periods when eczema is quiescent.

Chronic and relapsing eczema, severe pruritus, clinical signs, coexisting medical conditions, and dermatologic complications of atopic dermatitis lead to a decreased quality of life for patients and their families. These symptoms result in sleep disruption and decreased productivity at work or school, with detrimental effects on emotional and social life.¹³ Depression, anxiety, and suicidality have been associated with longstanding atopic dermatitis.¹⁴

DIAGNOSIS

The clinical diagnosis of atopic dermatitis is based on the morphologic features and distribu-

tion of skin lesions, the presence of associated clinical signs, and a characteristic medical history.¹⁵ A list of 23 clinical signs and symptoms of atopic dermatitis was published by Hanifin and Rajka in 1980 and is still used as a benchmark in clinical research. The American Academy of Dermatology has established core features used to diagnose the disease (Table 1).¹⁵ The severity of atopic dermatitis can be quantitated with the use of multi-item scoring tools such as the Eczema Area and Severity Index (EASI) and the Scoring Atopic Dermatitis (SCORAD) scale;¹⁶ both are used in practice and in clinical trials.¹⁶ The EASI assesses the severity of redness, thickness, excoriation, and lichenification and the percentage of skin involvement in four body areas (the head, trunk, arms, and legs). The scores

are summed, for an overall score ranging from 0 to 72. An EASI score of 7 or lower is considered to indicate mild disease, 8 to 21 moderate disease, 22 to 50 severe disease, and 51 to 72 very severe disease. The SCORAD score takes into account more lesion types and body areas than the EASI score and is calculated on the basis of the area of skin involved and the severity of redness, swelling, oozing, crusting, lichenification, and dryness, assessed separately for the head and neck, arms and legs, anterior trunk, back, and genitals. The score includes patient-reported symptom severity on the basis of two 100-point visual analogue scales, one for sleep loss and one for pruritus. The total score ranges from 0 to 103, with a score of 25 or lower indicating mild disease, 26 to 50 moderate disease, and 51 to 103 severe disease.¹⁶

COEXISTING CONDITIONS

Patients with atopic dermatitis are at risk for an “atopic march,” the sequential development of allergic disorders, including food allergies (especially in children), allergic rhinitis, rhinoconjunctivitis, and asthma.¹⁷ This apparent induction of allergies has been considered to be related to skin barrier leakage, with penetration of allergens and a predisposition of the immune system to react to the allergens with a response in CD4+ type 2 helper T (Th2) cells and subsequent B-cell antibody production. Patients of any age with atopic dermatitis are at risk for the development of bacterial, viral, or fungal skin infections due to skin barrier defects, bacterial skin colonization (especially by *Staphylococcus aureus*), and an altered skin microbiome.^{18,19} Common skin infections in patients with atopic dermatitis are *S. aureus*-induced infections (impetigo and abscesses), herpes simplex virus 1-related eczema herpeticum (Fig. 1H), and molluscum contagiosum infection.^{18,20,21} Fungal infections such as candidiasis of the skin or nails can also occur.¹⁹ Because of skin infections, patients with atopic dermatitis have a higher risk of life-threatening systemic infections (e.g., osteomyelitis, septic arthritis, and endocarditis) than patients who do not have atopic dermatitis, although such complications are rare.^{18,22} Other disorders that have been associated to varying extents with atopic dermatitis are inflammatory bowel disease and rheumatoid arthri-

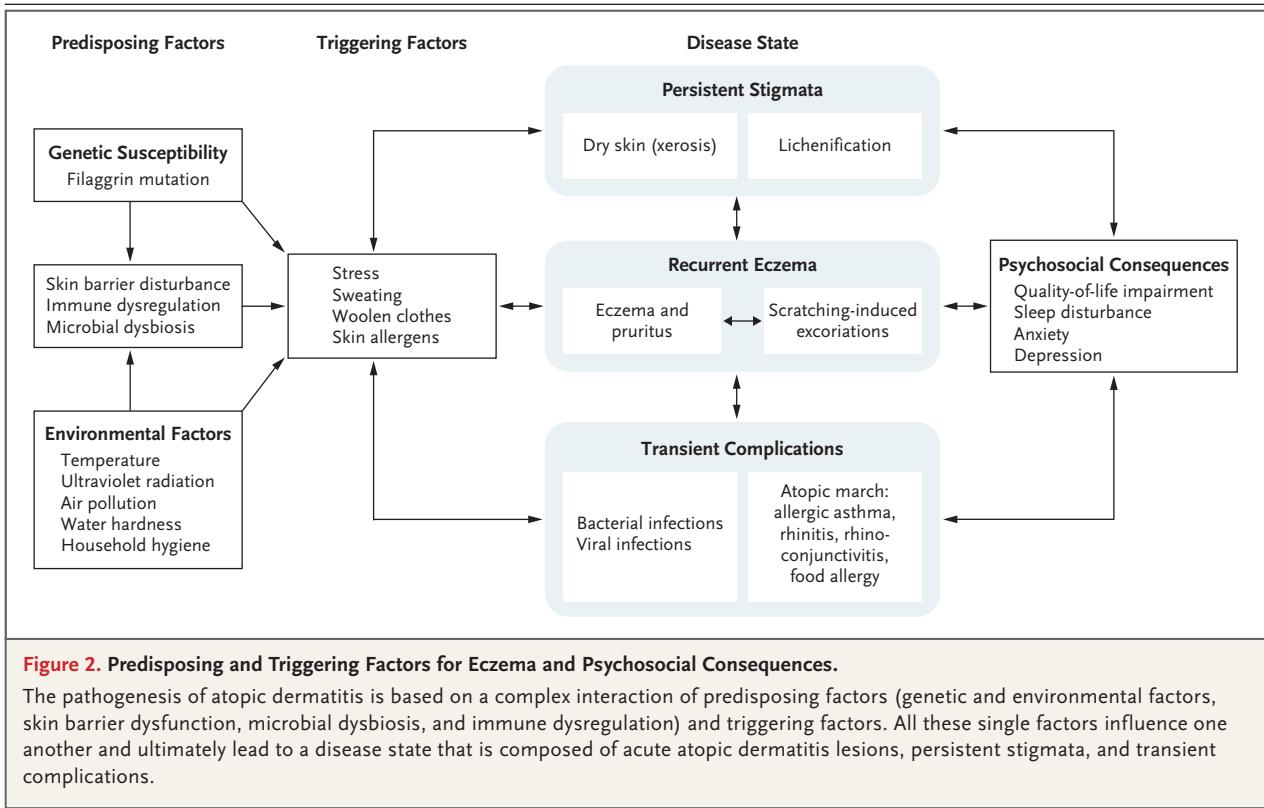
tis. A risk of cardiovascular diseases has been suggested, but estimates of this risk have varied.^{14,23}

PATHOGENESIS

Interactions among genetic and environmental factors, skin barrier dysfunction, microbial imbalance, immune dysregulation, and environmental triggers of skin inflammation play a role in the pathogenesis of atopic dermatitis (Fig. 2).²⁴⁻²⁶ Inflammation is thought to be initiated by disruption of the epidermal barrier and activation of epidermal inflammatory dendritic and innate lymphoid cells, which attract and interact with invading Th2 cells. The proximate mechanism for eczematous lesions is inflammation related to dysregulation of Th2 cells.²⁶ Activated T cells release cytokines into the skin, mainly interleukin-4, interleukin-13, and interleukin-31, which activate downstream Janus kinase (JAK) pathways. The cytokines promote inflammation, pruritus, and the production of antigen-specific IgE by activating B cells and plasma cells.

Studies have identified other immunotypes, such as those associated with activation of other helper T-cell pathways (i.e., Th1, Th17, and Th22), in part associated with race or ethnic group.¹¹ For example, activation of the Th2 and Th17 pathways has been reported in Asian patients, whereas in patients of European ancestry, there is mostly activation of the Th2 pathway. Activation of the Th1 and Th17 pathways is also absent in Black patients with atopic dermatitis.⁸ These differences may explain the various manifestations of eczematous lesions according to race or ethnic group. However, targeting mediators and cytokines in the Th2 pathway seems to be the most promising individualized approach to treatment.²⁷⁻²⁹

Among the genetic factors that promote skin barrier dysfunction, mutations in the filaggrin gene (*FLG*) have emerged as the most prominent, affecting 30 to 50% of White patients.²⁵ Filaggrin, which is produced by upper-layer epidermal keratinocytes, promotes the production of natural moisturizing factors and the lipid matrix, which acts like mortar, keeping keratinocytes in the horny layer together. A loss-of-function mutation in *FLG* leads to disturbed skin barrier formation and increased transepidermal water loss, resulting in dry skin. The lack of skin lipids



also reduces production of epidermal antimicrobial peptides, leading to increased microbial dysbiosis.^{25,26} This disturbance in the skin barrier makes it possible for allergens to penetrate the skin and induces allergic sensitization.

Environmental factors play a role in a predisposition to, and worsening of, atopic dermatitis. Established factors include extreme temperatures, ultraviolet radiation exposure, air pollution exposure (through activation of the epidermal aryl hydrocarbon receptor), increased water hardness, and increased frequency of household product use.²⁴ The last of these factors refers to the “hygiene hypothesis,” which proposes that increasing cleanliness leads to the decreasing incidence of infections in Western countries, which is associated with the increasing incidence of allergic and autoimmune diseases, including atopic dermatitis.²⁴ A study of the skin microbiome in patients with atopic dermatitis has shown that it is predominantly colonized by pathogenic *S. aureus*.²⁴ This shift in the microbiome, together with the reduced production of epidermal antimicrobial peptides, may have clinical implications for the development of impetigo and skin abscesses in areas of eczema.

Pruritus in atopic dermatitis is based on signaling between pruritogens released by keratinocytes, mast cells, and immune cells (T cells and eosinophils) and the small sensory-nerve fibers in the skin. The pruritogens comprise Th2 cytokines (especially interleukin-4, -13, and -31), thymic stromal lymphopoietin (an epithelium-derived proinflammatory cytokine), histamine, proteases, and neuropeptides. These pruritogens bind to receptors on sensory C-nerve fibers and A δ -nerve fibers in the epidermis and dermis, which sense pruritus and pain. Patients with atopic dermatitis frequently report painful sensations, including burning and stinging, in addition to pruritus, in eczematous skin regions.³⁰ The majority of pruritogens bind to nonhistaminergic nerve fibers. A small subgroup (<5%) of skin C-nerve fibers are histamine-sensitive; however, blocking histamine 1 receptors with antihistamines has not led to control of pruritus. Accordingly, guidelines do not recommend histamine 1 receptor antihistamines for pruritus control.³¹

Pruritogens are released not only by inflammation but also by scratching. This might result in hypersensitization of nerve fibers due to the

Table 2. Therapeutic Strategies for Atopic Dermatitis in Children and Adults.*

Strategy	Measures or Agent	Stage of Atopic Dermatitis (Age Limitation)
General		
Decolonization	Education about personal daily skin care and hygiene practices, frequent hand washing with soap and water, daily bathing or showering, avoiding reuse or sharing of personal hygiene items that contact the skin, avoiding contamination of topical medications and moisturizers, environmental hygiene measures (cleaning of surfaces, equipment, devices), wearing silver-coated clothing (for its antibacterial properties)	All stages
Therapy for skin infection, if necessary	Depends on the infection (e.g., topical disinfectants, systemic antibiotics, systemic acyclovir, removal of molluscum contagiosum)	All stages
Basic wound care	Covering open or weeping wounds	All stages
Avoidance of triggers	Reducing allergen exposure, for example	All stages
Education	Using behavioral therapy techniques, relaxation techniques, educational measures for affected adults and parents of affected children	All stages
Topical therapies		
Emollients	Moisturizers with a hydrophilic base, emollients with urea, bath oils, shower gels, wet-wrap therapy (increases penetration of topical agents, decreases water loss)	All stages (emollients with urea not used in children ≤5 yr)
Antipruritic agents containing emollients	Menthol and menthol derivatives, polidocanol, or lidocaine	All stages
Immunosuppressants	Glucocorticoids, calcineurin inhibitors (pimecrolimus, tacrolimus), phosphodiesterase-4 inhibitor (crisaborole)	All stages; choice of glucocorticoid class depends on patient's age and severity of atopic dermatitis
Topical therapies, not yet approved		
JAK inhibitors	Cerdulatinib (pan-JAK, SYK), delgocitinib (pan-JAK), ruxolitinib (JAK1 and JAK2), tofacitinib (JAK1 and JAK3) †	
Aryl hydrocarbon receptor inhibitor	Tapinarof	
Systemic therapies		
Ultraviolet phototherapy	Narrow-band UVB (311–313 nm), UVA1 (340–400 nm)	Moderate (rarely used in prepubertal children)
Immunosuppressants (oral or subcutaneous)	Azathioprine, glucocorticoids (only short courses), cyclosporine, methotrexate	Severe; should be maintained during coronavirus pandemic ³⁹
Biologic therapy (subcutaneous)	Interleukin-4Rα antagonist (dupilumab)	Severe (≥6 yr)
JAK inhibitor (oral)	Baricitinib (JAK1 and JAK2) †	Moderate to severe (adults)
Potential systemic therapies (not yet approved)		
JAK inhibitors (oral)	Abrocitinib (JAK1), gusacitinib (pan-JAK, SYK), tofacitinib (JAK1 and JAK3), upadacitinib (JAK1) †	
Interleukin-13 receptor antibodies (subcutaneous)	Lebrikizumab, tralokinumab	
Interleukin-22 receptor antibody (intravenous)	Fezakinumab	
Interleukin-31 receptor A antibody (subcutaneous)	Nemolizumab	
Interleukin-33 receptor A antibody (intravenous)	Etokimab	
Phosphodiesterase-4 inhibitor (oral)	Roflumilast	

* Information about therapeutic strategies is from Sidbury et al.,³⁵ Wollenberg et al.,³⁶ Wollenberg et al.,³⁷ and Eichenfield et al.³⁸ JAK denotes Janus kinase, SYK spleen tyrosine kinase, UVA1 ultraviolet A1, and UVB ultraviolet B.

† Targets of JAK inhibitors are shown in parentheses.

itch–scratch cycle, a hypothesis that is consistent with reports by patients of increased pruritus after scratching to relieve itch.^{32,33} The interleukin-4 α receptor subunit is expressed on pruritus-sensing nerve fibers and may hypersensitize them to pruritus on continuous stimulation with interleukin-4.³⁴ This might partly explain the itch–scratch cycle and the rapid benefit from inhibition of downstream JAK1 and JAK2 and the interleukin-4 α receptor pathways.

TREATMENT

Therapy for atopic dermatitis is selected according to the clinical stage of disease (mild, moderate, or severe), the extent of body-surface area involved, age, coexisting conditions and medications being taken by the patient, the severity of pruritus, the degree to which quality of life is impaired, and the goals of the patient.^{35,36} For all disease stages, including eczema-free intervals, general measures such as the use of emollients (with or without antipruritic agents) and avoidance of infections and trigger factors are advised (Table 2). When eczema occurs, the use of topical immunosuppressive therapies is recommended as a first approach. Crisaborole, a phosphodiesterase-4 inhibitor, has recently been approved for treatment of atopic dermatitis in the United States, but it is not available in all countries. For moderate eczema, ultraviolet phototherapy can be applied, but it is not used in children and young adults because of the potential for the development of skin cancer with long-term use. For severe atopic dermatitis, several conventional systemic immunosuppressants such as glucocorticoids, cyclosporine, or methotrexate have been used. However, these agents do not target specific points of immune dysregulation in atopic dermatitis and may result in severe adverse events, including liver and kidney dysfunction.

Regarding the coronavirus disease 2019 (Covid-19) pandemic, most dermatologic societies, including the American Academy of Dermatology, recommend that patients with atopic dermatitis continue to receive systemic immunosuppressive therapy unless they have a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For patients with a posi-

tive test, systemic immunosuppressive therapy can be reinitiated after recovery from Covid-19.⁴⁰

There has been progress in the development of Th2-targeted therapies. Promising agents are monoclonal interleukin-4, -13, -22, and -31 receptor antibodies, phosphodiesterase-4 inhibitors, and JAK inhibitors (topical and systemic), most of which have been tested in phase 2–3 trials. In a comparative study, the interleukin-4 antibody dupilumab and the JAK inhibitor abrocitinib both were associated with reductions in signs and symptoms of atopic dermatitis as compared with placebo; abrocitinib was superior to dupilumab in reduction of itch at 2 weeks, but otherwise the two drugs had similar outcomes.⁴¹ Adverse effects such as skin infections or worsening of asthma necessitate careful evaluation of the future use of these new therapies in sensitive populations (children) and in patients with typical complications of atopic dermatitis. For example, many patients have long-term, functionally impairing conjunctivitis with dupilumab therapy, especially when it is combined with seasonal allergic conjunctivitis. JAK inhibitors carry a risk of thromboembolism and cancer⁴² and may be associated with respiratory tract infections, herpes zoster infection, headache, nausea, diarrhea, and a decrease in the white-cell count.⁴³

CONCLUSIONS

Atopic dermatitis is a burdensome skin disease, particularly in children. Geographic and race or ethnic group variations, as well as a complex pathogenesis, have impeded the development of targeted therapies. Pruritus associated with the disorder affects quality of life and is a focus of treatment and a determinant of treatment efficacy, as well as a primary concern in the development of new medications to treat atopic dermatitis.

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