Chapter 12
Atopic Dermatitis

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Abstract

Atopic dermatitis is a chronic inflammatory skin disease defined by pruritic lesions, a disrupted epidermal barrier, and systemic immune dysregulation. Recent research highlights the critical role of microbiome dysbiosis and the "atopic march," where early skin barrier failure often leads to subsequent respiratory allergies. While genetic and environmental factors drive the pathogenesis, many childhood cases resolve significantly by adulthood. Management begins with rigorous skin hydration and topical corticosteroids to repair the barrier and reduce localized inflammation. For moderate to severe cases, the landscape has been transformed by targeted biologics and Janus kinase (JAK) inhibitors, which offer precise control over the underlying molecular pathways.

Keywords
Atopic dermatitis; Eczema; Pruritus; Epidermal barriers; Biologics; Janus kinase inhibitors; Type 2 inflammation.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic skin lesions, disrupted skin barrier function, dysregulation of the immune system, and allergic reactions to food and environmental allergens. AD generally presents in early childhood with often familial onset. Scratching at the area of pruritus leads to redness, cracking, scaling, and potential superinfection of the skin. Most patients with AD have a personal or family history of atopy (allergic rhinitis, allergic conjunctivitis, AD, or asthma).

The word "atopy" can be defined as a hypersensitivity of skin and mucous membranes against environmental substances, associated with increased immunoglobulin E (IgE) production and/or altered nonspecific reactivity in different organ systems, for example, skin in the case of AD and lung in the case of asthma. It is a chronic, highly pruritic, inflammatory skin disease frequently seen in patients with a history of respiratory allergy and allergic rhinitis. The prevalence of AD in children has been steadily increasing since the 1920s and now affects approximately 10-20% of children and 2-10% of adults at some point during their lifetime.

The term atopic dermatitis was first introduced in 1933 in recognition of the close association between AD and respiratory allergy. Recent studies suggest that the mechanisms underlying asthma and AD have greater similarities than differences, with infantile AD being closely linked to the subsequent onset of childhood asthma, allergic rhinitis, and food allergies, collectively known as the "atopic march". AD is ranked 15th in terms of the global disease burden. AD is a common, potentially debilitating condition that can compromise quality of life. Its most frequent symptom is pruritus.

Treatment should be directed at limiting itching, repairing the skin, and decreasing inflammation when necessary. Traditional therapies including lubricants, antihistamines, and topical corticosteroids remain the mainstays of initial therapy. However, the therapeutic landscape has evolved dramatically in recent years with the approval of novel topical treatments including Janus kinase (JAK) inhibitors (ruxolitinib, delgocitinib), PDE4 inhibitors (crisaborole, roflumilast), and aryl hydrocarbon receptor agonists (tapinarof). For systemic therapy, biologics targeting IL-4/IL-13 pathways (dupilumab, tralokinumab, lebrikizumab) and IL-31 receptor (nemolizumab), as well as oral JAK inhibitors (upadacitinib, abrocitinib, baricitinib) have revolutionized the treatment of moderate to severe AD.

Immunologic disturbances are reflected in the elevated IgE production and T-cell dysregulation observed in AD. Nonspecific altered reactivity is reflected in increased releasability of chemical mediator secreting cells and bronchial, nasal, and skin hyperreactivity. Each disease in the atopic triad—eczema/AD, bronchial asthma, and allergic rhinitis/hay fever—shares important immunological similarities, involving different areas of immunological influence. For example, AD affects the skin-associated lymphoid tissue, whereas asthma affects the bronchus-associated lymphoid tissue.

Pathogenesis

AD is a condition that requires interplay from several factors to explain its pathogenesis. Defects in epidermal barriers, dysregulation of various types of immune responses, genetic polymorphisms, and environmental factors have been implicated in the pathogenesis of the disease. The pathogenesis of AD is crucially influenced by three main factors: dysregulation of the immune response, barrier dysfunction, and pruritus.

An understanding of the relative contributions of allergens, IgE, T cells with skin-homing capability, Langerhans cells, keratinocytes, eosinophils, mast cells, and newly recognized cell types including type 2 innate lymphoid cells (ILC2s), basophils, and macrophages to the inflammatory process in AD may lead to improved treatments for this potentially debilitating disease. The concept that AD has an immunologic basis is supported by the observation that patients with primary T-cell immunodeficiency disorders frequently

have elevated serum IgE levels, eosinophilia, and eczematoid skin lesions indistinguishable from AD.

In the lesional skin of AD, various innate immune cells, including Th2 cells, type 2 innate lymphoid cells (ILC2s), and basophils, produce Th2 cytokines including interleukin (IL)-4, IL-5, IL-13, and IL-31. Alarmins such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are produced by epidermal keratinocytes, amplifying type 2 inflammation. In the chronic phase, not only Th2 cells but also Th22 and Th17 cells increase in number, leading to suppression of filaggrin expression by IL-4, IL-13, and IL-22, which further deteriorates the epidermal barrier function.

IL-31, a type 2 cytokine produced mainly by Th2 cells, has emerged as a key player in AD pathogenesis. IL-31 induces pruritus by acting on sensory neurons in the skin through the IL-31 receptor alpha chain (IL-31RA). Recent research has revealed that IL-31 also acts as an immunoregulatory factor that limits the magnitude of type 2 inflammatory responses in skin through neurogenic inflammation pathways. A network comprising macrophages expressing IL-31, TSLP, periostin, and basophils has been identified as significant in the manifestation of itching in AD.

Recent studies have demonstrated increased frequency of allergen-specific T cells producing increased IL-4 and IL-5 but little IFN-gamma in the peripheral blood and skin lesions of patients with AD. The majority of allergen-specific T-cell clones are TH0-type cells with the potential for development into either TH1 or TH2 cells after they have infiltrated into the skin. The ability of these T cells to develop into the TH1 or TH2 pathway is dependent on the cytokine milieu in which T-cell development is taking place, the host's genetic background, pharmacologic factors, and the costimulatory signals used during T-cell activation.

Defective Epidermal Barrier

The epidermis has four layers. The outermost layer, called the stratum corneum, serves as a barrier to decrease water evaporation and penetration of exogenous allergens and microbes. The stratum corneum is composed of cells that have keratin proteins and structural components, such as ceramides, filaggrin, and lipids. Filaggrin protein (FLG) plays a crucial role in maintaining the structure of the epidermis by aggregating keratin filaments to form a cytoskeleton in epidermal cells.

FLG is released from keratohyalin F granules as an inactive form and is converted to an active form by proteolysis and dephosphorylation. Studies have found that mutations in the FLG gene, specifically R501X and 2282del4, can induce a decrease of natural moisturizing factors, including sodium pyrrolidone carboxylic acid, urocanic acid, and

lipoprotein components, especially ceramides. A meta-analysis has confirmed that these mutations represent the most compelling genetic risk for AD. The alteration of the epidermal structure from this protein mutation leads to transepidermal water loss and evaporation, resulting in dry skin and itching.

Notably, FLG expression may be reduced in patients with AD without FLG mutations. Type 2 inflammatory mediators, including IL-4, IL-13, IL-31, IL-33, and TSLP, reduce FLG expression. Apart from FLG, a decrease of SPINK5 gene expression, which encodes Kazal-type 5 serine protease inhibitor, can increase cleavage of intercellular attachments in the stratum corneum and can compromise barrier function. In addition, decreased expression of epidermal claudin-1, a transmembrane protein component of tight junctions, can cause an impairment in tight junctions, which leads to skin barrier dysfunction in patients with AD.

Dysregulation of Cutaneous Immune Response

Thymic stromal lymphopoietin (TSLP) plays an important role in AD. TSLP expression in keratinocytes is induced by mechanical injury and stimulation of Toll-like receptors 2, 5, and 6. TSLP activates dendritic cells, which leads to proliferation of CD4 T cells that then differentiate into T-helper cell type 2 (TH2). Next, inflammatory cytokines, such as interleukin (IL)-4, IL-5, and IL-13, are produced and released. Furthermore, TSLP stimulates mast cells, basophils, and eosinophils, which play a crucial role in cutaneous inflammation.

It has been shown that scratching can induce TSLP expression and aggravate the course of AD, resulting in a vicious cycle of itching, scratching, TSLP expression, and TH2 upregulation. Furthermore, TH2 cells produce IL-31, which provokes pruritus. TH17 cells, which can produce IL-17 and IL-22, also are involved in AD pathogenesis. TH17 cells are normally found in acutely inflamed skin lesions. An increase in the number of TH17 cells correlates with the severity of AD. In a mouse model, FLG deficiency led to TH17-dominated skin inflammation. In addition, IL-22 induces epidermal hyperplasia that can lead to epidermal acanthosis in the chronic stages of AD.

Recent research has identified type 2 innate lymphoid cells (ILC2s) as important sources of IL-13 and lower levels of IL-4 in AD pathogenesis. Additionally, macrophages have been recognized as significant contributors to AD, with M2 macrophages being significantly increased in AD lesion areas. Spatial transcriptomics combined with single-cell RNA sequencing has identified potential cellular crosstalk between M2 macrophages expressing CCL13 and CCL18 and CD45RO+ T lymphocytes in AD lesions, promoting type 2 inflammation.

Immunohistology

The histologic features of AD depend on the acuity of the skin lesion. Uninvolved or clinically normal-appearing skin of patients with AD is histologically abnormal and demonstrates mild hyperkeratosis and a sparse perivascular cellular infiltrate consisting primarily of T lymphocytes. Acute lesions are characterized by marked intercellular edema (spongiosis) of the epidermis and a sparse epidermal infiltrate consisting primarily of T lymphocytes. In the dermis, there is a marked perivenular inflammatory cell infiltrate consisting predominantly of T lymphocytes and occasional monocyte/macrophages. Essentially all T cells infiltrating into the skin lesion express high levels of cutaneous lymphocyte antigen (CLA), which functions as a skin-homing receptor for T lymphocytes. Eosinophils, basophils, and neutrophils are rarely present in the acute lesion. Mast cells, in various stages of degranulation, are present in normal numbers.

In chronic lichenified lesions, the epidermis is hyperplastic with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing Langerhans cells in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells are increased in number but are generally fully granulated. Increased numbers of eosinophils are observed in chronic AD skin lesions. Although the role of eosinophils in the pathogenesis of AD is not completely understood, it is thought to contribute to tissue injury in AD through the production of reactive oxygen intermediates and release of cytotoxic granules. Recent studies have shown that IL-31 can induce release of pro-inflammatory cytokines and AD-related chemokines from eosinophils.

Cutaneous Infections: Role for Superantigens

Aside from food and inhalant allergens, fungal and bacterial skin infections exacerbate AD. Viral infections include herpes simplex, vaccinia, warts, molluscum contagiosum, and papilloma virus. The most common viral infection is herpes simplex, which tends to spread locally or can become generalized. Superficial fungal infections also appear to occur more frequently in atopic individuals. Recently there has been considerable interest in Malassezia furfur (also known as Pityrosporum ovale or Pityrosporum orbiculare) as a pathogen in AD. M. furfur is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against M. furfur are commonly found in patients with AD and most frequently in patients with head and neck dermatitis.

The greatest attention has focused on the contribution of Staphylococcus aureus colonization and infection to the severity of AD. S. aureus is found in more than 90% of

AD skin lesions. In contrast, only 5% of normal subjects harbor this organism and its localization is mainly in the nose and intertriginous areas. The importance of S. aureus in AD is supported by the observation that not only patients with impetiginized AD but also patients with AD without superinfection show clinical response to combined treatment with anti-staphylococcal antibiotics and topical corticosteroids.

Recent research has identified RNase 7 as abundantly expressed in keratinocytes and playing an important role in protecting human skin from *S. aureus* colonization. RNase inhibitor, which binds to RNase 7, is released by damaged keratinocytes, triggering inflammation in AD by inhibiting the ribonuclease and antimicrobial functions of RNase 7, which leads to RNA-mediated inflammation and S. aureus overgrowth.

S. aureus exacerbates or maintains skin inflammation in AD by secreting toxins known to act as superantigens, which stimulate marked activation of T cells and macrophages. Superantigens may induce an atopic process in the skin and have been demonstrated to induce T-cell expression of the skin-homing receptor through stimulation of IL-12 production. These mechanisms amplify the initial cutaneous inflammation in AD and create conditions favouring staphylococcal skin colonization. Peripheral blood mononuclear cells from children with AD have significantly higher proliferative responses to both S. aureus and Staphylococcal enterotoxin B as well as diminished production of IFN-gamma in response to S. aureus and Staphylococcal enterotoxin B.

The immunological and histopathological findings mentioned above are summarized and presented in Tables 12.1 to 12.8, divided into different aspects, taking into account the historical development of research, with supplementary information.

The Diagnosis

Atopy is universally recognized as a complex genotypic diathesis that manifests a syndrome of immunologic aberrations. It would indeed be an oxymoron to make the diagnosis of AD without establishing atopy in the personal or family history and examination. A history of atopy is best obtained by specifically asking for the recognized clinical signs and symptoms of the atopic triad and not by the confusing question: "Are you allergic?" In 1980 Hanifin and Rajka published diagnostic criteria for AD that have become universally accepted as the standard for the diagnosis of that clinical entity.

The diagnosis of AD can only be made by the presence of three essential criteria: personal or (first-degree) family history of atopy, pruritus, and eczema. Recent advances in understanding AD pathogenesis have led to improved assessment tools. Multiple scoring indices are now used to assess disease severity, including the Eczema Area and

Severity Index (EASI), the Scoring Atopic Dermatitis (SCORAD), the Patient-oriented Eczema Measure (POEM), and the Investigator's Global Assessment (IGA). The Harmonizing Outcome Measures for Eczema (HOME) initiative has recommended the use of the POEM index, as well as an updated version of the SCORAD known as the patient-oriented SCORAD index and the EASI.

Pruritus must be considered a quintessential feature of AD; pruritus is variable, fluctuating from mild to extremely intense. AD is an itch that when scratched erupts. If the atopic patient's itch is not rubbed or scratched, the skin may get red (vasodilate), but no eczema appears until it is traumatized. This can be described as an isomorphic response, or Koebner phenomenon. An erythema caused by certain histamine-releasing or vasodilatory foods (i.e., alcohol, spices) is a more common trigger of pruritus than the IgE-mediated reaction. Because the former is nonimmunologic, it is dose related and is not dependent on prior sensitization.

The itch in AD is mainly mediated via non-histaminergic pathways; thus, histamine and the respective bioactive amines contribute minimally to the itch pathogenesis, while type 2 cytokines (IL-4, IL-13, IL-31), epithelium alarmins (TSLP, IL-33, IL-25), neuropeptides, neurotrophins, the vicious "itch-scratch cycle," and microbiome dysbiosis with epithelium leakage, act synergistically. Despite the fact that histamine is the most abundant pruritogenic mediator in our body, its role as the major causation of itch in the patient with atopy remains questionable. Pruritus is the basic bane of atopic individuals.

Eczema is a nonspecific term often confounding the clinical and histopathologic description of various unrelated inflammatory diseases. The eczema of AD is the isomorphic response of scratching the itchy, atopic skin, and the clinical morphologic condition (oozy and/or vesicular and/or scaly and/or crusted and/or lichenified) is inherently never stationary and is constantly undergoing an evolutionary process (i.e., acute, subacute, and chronic).

Differential Diagnosis

We have to rule out some kinds of skin diseases as follows: infant seborrheic eczema, infant xerotic eczema, congenital ichthyosis including sex-linked recessive ichthyosis caused by steroid sulfatase deficiency, bullous congenital ichthyosiform erythroderma, scabies, pediatric dermatomyositis, mycosis fungoides (skin malignant lymphoma), photocontact dermatitis, contact dermatitis, chronic actinic dermatitis, and dermatitis due to Cryptomeria (cedar) pollen.

To ensure a thorough investigation, current clinical guidelines recommend that the following conditions also be considered in the differential diagnosis according to age group and underlying mechanism:

1. Immunological & Genetic Syndromes:

- Netherton Syndrome: Often misdiagnosed as severe AD in infancy. Characterized by the triad of ichthyosis linearis circumflexa, hair shaft defects (bamboo hair), and atopic features.
- Hyper-IgE Syndrome (Job Syndrome): Presents with eczematous dermatitis, but is distinguished by recurrent "cold" staphylococcal abscesses and distinct facial features.
- Wiskott-Aldrich Syndrome: Important to rule out in male infants with eczema, as it involves thrombocytopenia (look for petechiae) and recurrent infections.

2. Nutritional and Metabolic Disorders

Modern diets and malabsorption issues have brought these back to the forefront:

- Acrodermatitis Enteropathica: Zinc deficiency (either hereditary or acquired) that presents with periorificial and acral dermatitis.
- Phenylketonuria (PKU): Can present with an AD-like rash and pigmentary dilution.

3. Psoriasiform & Other Inflammatory Eruptions

- Psoriasis (specifically Pediatric Psoriasis): Can overlap significantly with AD (sometimes called "psoriatic dermatitis"). Look for more sharply demarcated plaques and involvement of the diaper area (which AD usually spares).
- Nummular Eczema: Often seen in adults; characterized by coin-shaped, highly pruritic lesions rather than the typical flexural distribution of AD.

4. Environmental and Infectious Mimics

- Hand, Foot, and Mouth Disease (HFMD): In patients with existing AD, the Coxsackievirus can cause Eczema Coxsackium, which looks like a severe AD flare but is actually a viral superinfection.
- Drug-Induced Dermatitis: Especially in older patients, certain systemic medications can trigger eczematous eruptions that mimic AD.

Assessment of Disease Severity

To assess the severity and extent of AD, several validated parameters are used. The Harmonizing Outcome Measures for Eczema (HOME) initiative has recommended core outcome measures that should be used in clinical practice and trials: the Eczema Area and Severity Index (EASI) for clinical signs, and the Patient-Oriented Eczema Measure (POEM) for patient-reported symptoms.

EASI (Eczema Area and Severity Index)
EASI assesses four clinical signs (erythema, infiltration/papulation, excoriation, and lichenification) in four body regions (head/neck, upper limbs, trunk, lower limbs), with scores ranging from 0 to 72. Updated severity strata based on validation studies are:

- Clear: 0
- Almost clear: 0.1-1.0
- Mild: 1.1-7.0
- Moderate: 7.1-21.0
- Severe: 21.1-50.0
- Very severe: 50.1-72.0

EASI heavily weights disease extent (~50%), making it particularly useful for tracking treatment response in moderate-to-severe disease. However, EASI scores ≤5 have limited discriminative ability and may not distinguish between severe localized lesions and mild extensive lesions. For optimal reliability, the same clinician should perform both baseline and follow-up assessments.

SCORAD (Scoring Atopic Dermatitis)
SCORAD combines three components: (1) affected surface area (A, 0-100%); (2) intensity of six clinical signs (erythema, edema, excoriation, oozing/crusting, lichenification, and xerosis; B, 0-18); and (3) subjective symptoms of pruritus and sleep disturbance (C, 0-20). The SCORAD is calculated as A/5 + 7B/2 + C, with total scores ranging from 0 to 103.

Updated severity strata based on recent validation studies are:

- Clear: 0-9.9
- Mild: 10.0-28.9
- Moderate: 29.0-48.9
- Severe: 49.0-103

Unlike EASI, SCORAD is primarily driven by lesional intensity (~60%) with smaller weighting for extent (~20%), and uniquely assesses xerosis and subjective symptoms. A patient-oriented version (PO-SCORAD) omits the subjective symptoms component, with severity strata: mild 0-27, moderate 28-56, severe 57-104.

POEM (Patient-Oriented Eczema Measure)
POEM is the HOME initiative's recommended patient-reported outcome for assessing AD symptoms. It evaluates seven symptoms over the past week (itch, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness) with scores from 0 to 28.

Validated severity strata are:

- Clear/almost clear: 0-2
- Mild: 3-7
- Moderate: 8-16
- Severe: 17-24
- Very severe: 25-28

Alternative three-tier stratification used in some population-based studies: mild 0-7, moderate 8-19, severe 20-28. POEM is particularly valuable as it is entirely patient-derived and correlates well with quality of life measures.

Other Assessment Tools
The Investigator's Global Assessment (IGA) provides a rapid single-score assessment of overall severity (typically on a 0-4 scale: clear, almost clear, mild, moderate, severe) but does not account for disease extent. Body Surface Area (BSA) quantifies disease extent but not intensity. The Rajka-Langeland grading (scores 3-9) uniquely incorporates disease course over the past year alongside sleep disturbance and extent.

Practical Clinical Considerations
Clinicians should recognize that EASI and SCORAD measure fundamentally different disease constructs. EASI correlates nonlinearly with SCORAD, particularly at lower severity levels. For comprehensive assessment, combining physician-assessed measures (EASI or SCORAD) with patient-reported outcomes (POEM) provides complementary information on disease impact. The choice of tool should match the clinical context: EASI for clinical trials and moderate-to-severe disease monitoring, SCORAD when assessing subjective burden is important, and POEM for routine symptom tracking and patient engagement.

Complications

When managing atopic dermatitis, it is essential to monitor for common infectious complications such as Kaposi varicelliform eruption, streptococcal impetigo, and body trichophytosis. Beyond these dermatologic concerns, current clinical evidence

increasingly characterizes atopic dermatitis as a systemic inflammatory disease associated with comorbidities such as atopic alopecia, eosinophilic esophagitis, and an elevated risk of thyroid disorders and systemic lupus erythematosus. Furthermore, the significant impact on neuropsychiatric health—manifesting as chronic sleep fragmentation, anxiety, and depression—is now recognized as a primary driver of patient morbidity. While the overall safety profile of modern targeted treatments remains favourable, latest pharmacovigilance data necessitates careful monitoring for rare adverse events, particularly the increased risk of herpes zoster and specific laboratory abnormalities associated with Janus kinase (JAK) inhibitors and other emerging biologic therapies.

The Treatment

The management of AD has transitioned from a strategy of broad immunosuppression to one of precision medicine. At the core of this evolution is the understanding that AD is not merely a "dry skin" condition, but a complex immunological failure characterized by epidermal barrier dysfunction, immune dysregulation, and microbial dysbiosis.

Education of patients and families is one of the most effective foundational interventions for AD. Information about avoidance of irritants and allergens is critical in preventing AD exacerbations, and written eczema action plans may be beneficial by enabling eczema self-management, reminding patients and caregivers of maintenance regimens and additional therapies to incorporate during flares. The American Academy of Dermatology (AAD) and Joint Council of Allergy, Asthma, and Immunology (AAAAI and ACAAI) have published updated guidelines of care for AD, with a 2024 focused update incorporating evidence for novel topical small molecule and biologic therapies including tapinarof cream, roflumilast cream, lebrikizumab, and nemolizumab.

The treatment of AD consists of five pivotal structures: (1) Avoidance of allergens, (2) Skin care (skin hydration, moisturizers, phototherapy), (3) Avoidance of irritants/treatment for pruritus and deterrent to skin scratching, (4) Antiallergic inflammation (topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors, topical PDE4 inhibitors, and other targeted topical treatments), and (5) Exclusion of exacerbation factors (appropriate skin care and avoidance of subclinical infections). Management begins with rigorous skin hydration and topical corticosteroids to repair the barrier and reduce localized inflammation. These foundational steps address the immediate epidermal defects—including filaggrin deficiency and disrupted tight junction proteins—preventing the penetration of environmental triggers that exacerbate the "atopic march." Importantly, proactive maintenance therapy with emollients has been shown to reduce flare frequency and the overall burden of disease, making barrier repair not merely reactive but preventive.

For moderate to severe cases, the landscape has been transformed by targeted biologics and Janus kinase (JAK) inhibitors, which offer precise control over the underlying molecular pathways. Treatment options now include systemic biologics targeting IL-4/IL-13 pathways (dupilumab, tralokinumab, lebrikizumab), IL-31 receptor (nemolizumab), and oral JAK inhibitors (upadacitinib, abrocitinib, baricitinib). Unlike traditional systemic immunosuppressants—such as cyclosporine, methotrexate, and azathioprine—these modern interventions home in on specific signaling molecules like IL-4 and IL-13 (the Th2 axis central to AD pathophysiology), as well as IL-31 (a key pruritogenic cytokine), which are the primary drivers of Type 2 inflammation. This targeted approach allows for significant disease clearance while minimizing systemic side effects, with rapid improvement in both objective disease severity scores (such as EASI and IGA) and patient-reported outcomes, particularly pruritus. Additionally, emerging evidence suggests these therapies may interrupt the atopic march by addressing the systemic immune dysfunction that links AD to subsequent allergic rhinitis and asthma.

By integrating these advanced therapies with traditional topical care and addressing common comorbidities—including secondary bacterial colonization with Staphylococcus aureus, eczema herpeticum risk, and psychosocial impacts—clinicians can now offer patients a more tailored, effective, and sustainable long-term management plan. The treat-to-target approach, increasingly adopted from allergy and immunology, emphasizes regular assessment and therapeutic adjustment to achieve and maintain disease control. The following sections detail a progressive therapeutic ladder, moving from essential topical maintenance to advanced systemic modulators, with consideration of patient age, disease phenotype, and individual treatment goals.

Avoidance of Allergens

Food allergens have been shown to play a role in a subset of patients with AD, with milk, egg, peanut, soy, wheat, and fish accounting for approximately 90% of the foods found to exacerbate AD. Removal of proven food allergens from the patient's diet can lead to significant clinical improvement. Serial measurements of specific IgE levels to several food allergens by the ImmunoCAP system have proved to be of value in following the natural history of patients' food allergies. The degree of sensitization to aeroallergens has also been shown to be associated with the severity of AD.

Role of superantigens due to cutaneous infections and importance of bathing and moisturizing practices in atopic dermatitis.

Atopic skin shows enhanced transepidermal water loss associated with impaired function of the water permeability barrier. Hydration of the skin is best accomplished through

soaking baths. Bathing might also reduce colonization by S. aureus. To prevent evaporative effects, patients need to apply medication or moisturizer immediately after bathing or wetting their skin within 3 minutes (the "3-minute rule").

The European Task Force on Atopic Dermatitis (ETFAD) policy document recommends moisturizers for all AD patients. Use of moisturizers together with hydration helps reestablish and preserve the stratum corneum barrier. Daily moisturizer therapy can increase skin hydration and improve water barrier function. Ceramide-dominant emollients added to standard therapy in children with refractory AD have shown improvements in transepidermal water loss, stratum corneum integrity, and hydration status.

Recent evidence supports that application of moisturizer to neonates prevents development of AD/eczema. A study showed that approximately 32% fewer neonates who received moisturizer had AD/eczema by week 32 compared to controls. Errors in bathing and moisturizing are a major cause of persistent AD. The choice of soap may not be very important, but use of proper, unfragranced moisturizers (ointments such as petrolatum, Neutrogena Hand Cream, Aquaphor, or creams such as Cetaphil, Vanicream, DML, Aveeno Moisture Cream) applied within 3 minutes after bathing is critical.

Aside from food and inhalant allergens, fungal, bacterial, and viral skin infections exacerbate AD. Viral infections include herpes simplex, vaccinia, warts, molluscum contagiosum, and papilloma virus. The most common viral infection is herpes simplex, which tends to spread locally or can become generalized, particularly in patients with deficient antimicrobial peptide expression. Superficial fungal infections also occur more frequently in atopic individuals. Recurrence of dermatophyte infections has been documented to coincide with AD flaring. Malassezia furfur (Pityrosporum ovale/orbiculare), a lipophilic yeast in seborrheic areas, generates IgE antibodies commonly in AD patients, most frequently in those with head and neck dermatitis.

The greatest attention focuses on Staphylococcus aureus colonization and infection contributing to AD severity. S. aureus colonizes 30-100% of AD skin lesions versus only 5% of normal subjects, localizing mainly to the nose and intertriginous areas. Recent studies demonstrate that nasal mucosa serves as the major reservoir, with 65% of patients showing matched colonization between nasal and skin sites. The importance of S. aureus is supported by clinical response to combined anti-staphylococcal antibiotics and topical corticosteroids, even in non-impetiginized AD.

S. aureus exacerbates skin inflammation through multiple mechanisms. Secreted toxins act as superantigens (staphylococcal enterotoxins A, B, C, D, E, and toxic shock syndrome toxin-1), stimulating marked T-cell and macrophage activation. Two-thirds of S. aureus isolates from lesional skin encode superantigens, with SEC and SEA being

most common. Greater than 80% of AD-associated S. aureus strains display highly abnormal and complex superantigen patterns. These superantigens penetrate inflamed skin, stimulating epidermal Langerhans cells and macrophages to produce IL-1, TNF, IL-12, TSLP, and IL-8, markedly amplifying cutaneous inflammation. Superantigens also induce T-cell expression of cutaneous lymphocyte antigen (CLA), the skin-homing receptor, promoting T-cell recruitment to skin.

Beyond superantigens, S. aureus produces multiple virulence factors. Alpha-toxin (α-hemolysin) induces keratinocyte cytotoxicity, with AD keratinocytes showing increased susceptibility due to reduced filaggrin and sphingomyelinase expression. Protein A activates TNF receptor-1 on keratinocytes, inducing TSLP and IL-8. Lipoproteins activate toll-like receptor-2, while phenol-soluble modulins and lipoteichoic acid contribute to inflammation. S. aureus proteases increase serine protease activity in keratinocytes, directly disrupting the skin barrier and facilitating dermal penetration.

Peripheral blood mononuclear cells from AD children show significantly higher proliferative responses to S. aureus and staphylococcal enterotoxin B, with diminished IFN-γ production but enhanced IL-4 production. This Th2-skewed response correlates with S. aureus penetration into dermis and increased expression of IL-4, IL-13, IL-17, IL-22, and TSLP. Impaired IFN-γ production results in failure to eradicate S. aureus, with decreased LL-37 (cathelicidin) antimicrobial peptide expression facilitating persistent colonization. S. aureus colonization density correlates with disease severity on both affected and unaffected skin, contributing to microbial dysbiosis and exacerbating Th2/Th17 polarization.

Persistence on skin contributes to inflammation through continued T-cell activation, proinflammatory mediator release, and corticosteroid resistance. Furthermore, by eliciting IgE responses to staphylococcal toxins, S. aureus can activate mast cells, basophils, and other FcεR-bearing cells, creating a feed-forward inflammatory loop. S. aureus also promotes allergen sensitization, food allergy development, and progression of the atopic march, increasing risk for invasive infections including impetigo, cellulitis, abscesses, and bacteremia.

Optimal skin care in AD emphasizes regular bathing and moisturization. Current guidelines (2024-2025) recommend daily to every-other-day bathing for 5-10 minutes with lukewarm water and gentle, fragrance-free cleansers. Dilute bleach baths (2-3 times weekly for 10 minutes) are recommended as adjuvant therapy for moderate-to-severe AD, providing antimicrobial and anti-inflammatory effects. Emollient bath additives, however, are no longer recommended, as recent evidence does not support their efficacy. Moisturizers should be applied liberally within 3 minutes after bathing while skin remains damp, improving the epidermal barrier and decreasing transepidermal water loss. Bland, fragrance-free, occlusive moisturizers reduce AD severity, decrease topical

medication use, and increase time between flares. Importantly, recent large trials (BEEP, PreventADALL) demonstrate that prophylactic moisturizers do not prevent AD development, contradicting earlier hypotheses. Proactive therapy with topical anti-inflammatory drugs (corticosteroids, calcineurin inhibitors, PDE-4 or JAK inhibitors) applied at earliest signs of inflammation effectively suppresses recurrent flares. This comprehensive approach addressing both microbial colonization and barrier dysfunction remains fundamental to AD management. Evidence regarding the role of staphylococcal superantigens in AD is presented in Table 12.9, and optimal bathing and moisturizing management is summarized in Table 12.10.

Avoidance of Irritancy

Patients with AD have a lowered threshold of irritant responsiveness and need to avoid irritancy. Environmental factors that can modulate the effect of irritancy include temperature, humidity, and texture of fabrics. Temperature in home and work environments should be temperate with moderate humidity to minimize sweating. Occlusive clothing should be avoided, and loose-fitting cotton or cotton blend garments should be substituted to help with overheating. The most important quality of clothing fabrics might be nonabrasiveness and breathability.

Treatment for Pruritus and Deterrent to Skin Scratching

Antihistaminic agents are variable for the treatment of pruritus and deterrent to skin scratching. The second-generation antihistaminic agents, such as cetirizine, loratadine, and fexofenadine, are good to take daytime without uncomfortable side effects (i.e., drowsiness, malaise, and dry mouth). However, they are not effective for the control of strong itching because AD itch is primarily non-histaminergic.

For strong itching, first-generation antihistaminic agents, such as diphenhydramine, chlorpheniramine, and hydroxyzine, are more effective. The strongest drug for the treatment of pruritus and deterrent to skin scratching is hydroxyzine. Administration of 30-50 mg of diphenhydramine hydrochloride three times a day or 25-50 mg of hydroxyzine pamoate before sleep for moderate to severe AD patients is effective to restrain involuntary scratching. Control of pruritus and deterrent to skin scratching during sleep is critically important because unconscious skin scratching is a potent exacerbation factor of AD.

Topical diphenhydramine ointment is also strongly effective for the control of pruritus without major side effects and is usually used with topical corticosteroids for the treatment of AD. Deterrence of skin scratching is critical for the treatment of AD, and

these different drugs should be used with accurate understanding of each drug's characteristics conforming to each patient's skin condition.

Topical Corticosteroids

Since their introduction approximately 50 years ago, topical corticosteroids (TCS) have been the mainstay of treatment for AD, showing efficacy in both acute and chronic disease. By acting on multiple resident and infiltrating cells, primarily through suppression of inflammatory genes, they are effective in reducing inflammation and pruritus. In addition, TCS might have an effect on bacterial colonization in AD, reducing the density of S. aureus.

TCS are available in extremely high (class 1) to low (class 7) potencies. Choice of which TCS preparation to prescribe depends on the severity and distribution of eczematous lesions. Using the least potent corticosteroid that is effective should be the general rule. In children, the fingertip unit (FTU) is defined as the amount of topical medication extending from the tip to the first joint on the palmar aspect of the index finger. Approximately 1 FTU is needed to cover the hand or groin, 2 FTUs for the face or foot, 3 FTUs for an arm, 6 FTUs for the leg, and 14 FTUs for the trunk.

TCS have typically been applied twice daily. Fluticasone propionate cream has been shown to be safe and effective in children and infants with AD as young as 3 months of age. Once daily treatment has been shown to be effective for topical fluticasone propionate and mometasone furoate. Several studies with fluticasone propionate have shown that once control is achieved with a once daily regimen, long-term control can be maintained with twice weekly therapy (proactive therapy approach).

However, a 2025 expert consensus panel has highlighted risks of TCS therapy and emphasized the role for advanced targeted topical treatments for inflammatory skin diseases. A position paper on systemic corticosteroid use in AD recommends minimizing their use due to safety concerns and the availability of safer targeted therapies.

Topical Calcineurin Inhibitors

Topical corticosteroids have been associated with adverse local effects such as dermal atrophy, striae, telangiectasia, perioral dermatitis, and acneiform eruptions, as well as a risk of systemic effects such as hypothalamic-pituitary-adrenal axis suppression. The development of nonsteroidal topical immunosuppressants has been a historic development in therapy of AD. Topical calcineurin inhibitors (TCI) are an important class of medications that have been shown to have clinical efficacy in AD.

Tacrolimus (Protopic ointment, 0.03% and 0.1%) is a potent immunosuppressant that inhibits the activation of key cells involved in AD including T cells, Langerhans cells, mast cells, and keratinocytes. Tacrolimus 0.03% and 0.1% ointments have been shown to be safe and effective in the treatment of children (older than 2 years of age) and adults with AD. Long-term studies showed decreased S. aureus colonization during long-term therapy with tacrolimus ointment, and cutaneous infection rates decreased with extended use.

Pimecrolimus (Elidel cream 1%) is an ascomycin derivative developed specifically to treat inflammatory skin conditions. Pimecrolimus works through inhibition of phosphorylase activity of the calcium-dependent serine/threonine phosphatase calcineurin. Multiple clinical studies have demonstrated the efficacy and safety of pimecrolimus 1% cream in AD. Long-term therapy with pimecrolimus for 6 months and 1 year has shown that early treatment of AD signs and symptoms with pimecrolimus can prevent disease progression by preventing flares.

Studies have shown that using pimecrolimus as a first-line pharmacologic agent to treat early signs and symptoms of AD prevents progression to more severe exacerbations in approximately 50% of cases, reducing the need for TCS. Neither skin atrophy nor hypothalamic-pituitary-adrenal axis suppression has been observed with TCI, making them more suitable than TCS for frequent or prolonged use, especially on larger body surfaces or on areas especially prone to atrophy with steroid use.

Topical JAK Inhibitors

Mechanism of Action and Rationale

Many of the cytokines involved in AD pathology, including IL-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin (TSLP), and IFN-γ, signal through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. The JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2); the STAT family includes STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6. Activation of the JAK-STAT pathway has been implicated in the pathology of several immune-mediated inflammatory diseases, including AD.

The rationale for topical JAK inhibition in AD is particularly compelling because this pathway represents a convergence point for multiple inflammatory cytokines. IL-4 and IL-13, the hallmark Th2 cytokines in AD, signal through JAK1/JAK3 and JAK1/JAK2/TYK2 respectively, activating STAT6 to promote barrier dysfunction, B cell class switching to IgE, and perpetuation of type 2 inflammation. IL-31, the primary pruritogenic cytokine in AD, signals through JAK1/JAK2 and directly activates sensory neurons, making JAK1 inhibition particularly effective for rapid itch relief. Additionally,

TSLP (signaling through JAK1/JAK2) and IL-22 (through JAK1/TYK2) contribute to barrier disruption and epidermal hyperplasia, respectively. By targeting these shared signaling nodes, topical JAK inhibitors offer broad-spectrum anti-inflammatory effects while avoiding the systemic immunosuppression and safety concerns associated with oral JAK inhibitors.

Ruxolitinib Cream

Ruxolitinib cream (Opzelura®), a JAK1/JAK2 inhibitor, was approved by the FDA in September 2021 for short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. In July 2024, the FDA expanded approval to include patients as young as 12 years of age. It leverages inhibition of the JAK1/JAK2 pathway with low concern for systemic toxicity due to minimal percutaneous absorption.

The pivotal TRuE-AD1 and TRuE-AD2 phase 3 trials demonstrated that ruxolitinib cream 1.5% achieved Investigator's Global Assessment (IGA) treatment success (IGA score of 0 or 1 with ≥2-grade improvement) in 50-54% of patients by week 8, compared to 15-23% with vehicle. Notably, significant itch reduction (≥4-point improvement in Peak Pruritus Numerical Rating Scale) occurred as early as week 1 in approximately 50% of patients, addressing one of the most debilitating symptoms of AD with rapid onset. Long-term safety data from the TRuE-AD3 extension study (52 weeks) showed sustained efficacy with intermittent use and no significant systemic immunosuppression, opportunistic infections, or laboratory abnormalities. Adolescent data from the TRuE-AD4 and TRuE-AD5 trials confirmed similar efficacy and safety in patients aged 12-17 years.

Pediatric studies have shown promising safety and efficacy in children aged 2 to 11 years, with no systemic accumulation or adverse events. The TRuE-AD6 study in patients aged 2-11 years demonstrated IGA treatment success rates of approximately 44% at week 4, with favorable safety profiles and no concerning systemic absorption even in younger children with higher body surface area involvement. Pharmacokinetic studies confirmed minimal systemic exposure, with plasma concentrations below quantifiable limits in most patients, supporting the localized mechanism of action.

Delgocitinib Ointment

Delgocitinib ointment (ANZUPGO®), a pan-JAK inhibitor (inhibiting JAK1, JAK2, JAK3, and TYK2), was approved by the FDA in July 2024 for topical treatment of moderate to severe chronic hand eczema and atopic dermatitis in adults. Delgocitinib has been used in Japan since June 2020 (under the brand name Corectim®) with favorable efficacy and safety profiles, providing extensive real-world evidence prior to US approval. The approval in the US expands topical treatment options for patients with AD, particularly those with recalcitrant disease or sensitive skin areas.

The pan-JAK inhibition profile of delgocitinib offers theoretical advantages over selective JAK inhibitors by simultaneously blocking all four JAK enzymes, thereby interrupting a broader spectrum of inflammatory cytokine signaling. Japanese phase 3 studies demonstrated that delgocitinib 0.5% ointment achieved significant improvements in Eczema Area and Severity Index (EASI) scores, with mean reductions of approximately 60-70% from baseline by week 4. The Modified Eczema Area and Severity Index (mEASI) response rates were superior to vehicle, with approximately 30-40% of patients achieving ≥75% improvement (mEASI-75) by week 4.

Importantly, delgocitinib has shown efficacy in difficult-to-treat areas such as facial and intertriginous AD, where traditional topical corticosteroids may be associated with adverse effects like skin atrophy and telangiectasia. The ointment vehicle provides enhanced barrier repair properties compared to cream formulations, making it particularly suitable for severely xerotic or fissured skin. Long-term Japanese registry data (up to 52 weeks) demonstrated sustained efficacy with continuous or intermittent application, with adverse event rates comparable to topical corticosteroids, predominantly application site reactions (mild burning or stinging in 5-10% of patients).

Comparative Considerations and Clinical Use

The availability of both ruxolitinib (JAK1/JAK2-selective) and delgocitinib (pan-JAK) provides clinicians with options based on disease severity, anatomical location, and patient preference. Ruxolitinib cream may be preferred for mild to moderate disease, sensitive skin areas (face, neck, intertriginous zones), and pediatric patients due to its established safety data across age groups. Delgocitinib ointment may be particularly useful for moderate to severe disease, lichenified plaques requiring enhanced emollient properties, hand eczema, and patients who have not responded adequately to selective JAK inhibitors or topical corticosteroids.

Both agents offer significant advantages over topical corticosteroids: no risk of skin atrophy, no tachyphylaxis with prolonged use, rapid onset of antipruritic effects, and suitability for proactive maintenance therapy in high-risk areas. However, both carry FDA boxed warnings regarding serious infections, malignancies, major adverse cardiovascular events, and thrombosis, mirroring the warnings for oral JAK inhibitors, although the clinical relevance of these warnings for topical formulations with minimal systemic absorption remains debated. Current evidence suggests these risks are theoretical for topical use, with no signal detected in clinical trials or post-marketing surveillance.

Emerging Topical JAK Inhibitors

Additional topical JAK inhibitors are in development or recently approved. Cerdulatinib (a dual JAK1/JAK3 and SYK inhibitor) and tofacitinib cream (a JAK1/JAK3-selective inhibitor) are in late-stage clinical trials, with phase 2/3 data showing efficacy comparable to ruxolitinib. The evolving landscape of topical JAK inhibition promises

increasingly tailored options for AD management, with potential for improved selectivity profiles, novel vehicle formulations, and combination strategies with barrier repair agents.

Clinical Integration

Topical JAK inhibitors represent a paradigm shift in AD management, offering steroid-sparing alternatives with distinct mechanisms of action. They are particularly valuable for: (1) patients requiring long-term facial or intertriginous area treatment, (2) those experiencing tachyphylaxis to topical corticosteroids, (3) rapid control of severe pruritus, and (4) proactive maintenance therapy in conjunction with emollients. The treat-to-target approach suggests early introduction of topical JAK inhibitors in moderate disease to achieve rapid disease control, followed by step-down to maintenance regimens. Integration with comprehensive skin care, trigger avoidance, and patient education optimizes long-term outcomes while minimizing treatment burden.

Topical PDE4 Inhibitors

Phosphodiesterase-4 (PDE4) inhibitors represent another class of nonsteroidal topical anti-inflammatory agents. By inhibiting the degradation of cyclic adenosine monophosphate by PDE4, these agents curtail T-cell signaling pathways and production of inflammatory cytokines.

Crisaborole (approved in 2016) was the first PDE4 inhibitor approved for dermatologic use. While it paved the way for this class, it faced challenges with tolerability, particularly application site burning and stinging.

Roflumilast cream 0.15% was approved by the FDA in July 2024 for the treatment of mild to moderate AD in individuals aged 6 years and older. In two parallel phase 3 randomized double-blind, vehicle-controlled trials (INTEGUMENT-1/INTEGUMENT-2), 32.0% and 28.9% of patients achieved the primary endpoint. Long-term extension data showed that proactive, twice-weekly use among individuals who achieved complete disease clearance was able to maintain disease control. Roflumilast offers ease of use with once-daily application and has no boxed warning, making it ideal for proactive, long-term management.

Aryl Hydrocarbon Receptor Agonists

Tapinarof 1% cream, an aryl hydrocarbon receptor (AhR) agonist, was approved for AD in 2024 (initially approved for psoriasis). Tapinarof shows promise for its potential remittive effect, allowing extended results even after treatment cessation. Phase 3 long-term extension data demonstrated that most patients achieved nearly clear or clear skin at

least once during the extended, flexible treatment period, with the possibility for multiple off-drug treatment weeks for patients achieving complete skin clearance. Tapinarof represents a novel mechanism of action in AD therapy targeting the AhR pathway.

Topical medications, including corticosteroids and non-corticosteroids for the treatment of AD, are outlined in Table 12.11.

Systemic Biologic Therapies

Dupilumab

Dupilumab, a fully human monoclonal antibody targeting interleukin-4 receptor alpha (IL-4Rα), was the first biologic approved for AD in 2017 and has revolutionized AD management. By blocking both IL-4 and IL-13 signaling, dupilumab addresses key pathways in type 2 inflammation. Dupilumab is now approved for patients aged 6 months and older, making it the most widely accessible biologic for pediatric patients.

Integrated analyses from multiple phase 3 clinical trials (>7000 patient-years) of dupilumab for treatment of children, adolescents, and adults with AD demonstrated a sustained safety profile. Real-world effectiveness studies have confirmed the efficacy of dupilumab across diverse patient populations. Recent data have shown catch-up in growth for pediatric AD patients within a few months of initiating treatment, and some children can maintain disease control with periods off drug after achieving stability.

Dupilumab has broader indications beyond AD, including asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and prurigo nodularis. This makes it particularly valuable for patients with multiple type 2 inflammatory conditions. The most common adverse events are injection-site reactions and ocular surface disease/conjunctivitis, which affects approximately 10-30% of patients. Recent pharmacovigilance studies have monitored for rare associations with cutaneous T-cell lymphoma, though causality remains unclear.

Tralokinumab

Tralokinumab is an IgG4 monoclonal antibody that selectively neutralizes IL-13 and was approved by the FDA in December 2021 for treating patients with moderate-to-severe AD aged 12 years and older. Tralokinumab prevents IL-13 from interacting with IL-13Rα1 and IL-13Rα2 receptors, thereby blocking IL-13 signalling.

Real-world data and clinical trials have demonstrated tralokinumab's efficacy in maintaining disease control, with particular effectiveness noted for head and neck AD.

Combined placebo-controlled and long-term extension data revealed remarkable control of head-and-neck disease among individuals on continuous therapy. Accumulating global reports show disease improvement after tralokinumab treatment in patients refractory to prior targeted systemic treatments.

Tralokinumab offers flexible maintenance dosing options (every 2 weeks or every 4 weeks after initial treatment), which may improve treatment adherence. Drug survival studies show favourable retention rates for tralokinumab. The most common adverse events are upper respiratory tract infections, conjunctivitis, and injection-site reactions. Tralokinumab generally has a lower incidence of conjunctivitis compared to dupilumab.

Lebrikizumab

Lebrikizumab, a high-affinity monoclonal antibody targeting IL-13, was approved by the FDA in September 2024 for moderate to severe AD in adolescents and adults aged 12 years and older. Lebrikizumab binds to IL-13 at a site that prevents the heterodimerization of IL-4Rα and IL-13Rα1, thereby inhibiting downstream signalling through the IL-4R; it does not bind to the IL-13Rα2 decoy receptor.

In parallel randomized double-blind placebo-controlled trials (ADvocate1/ADvocate2), 43.1% and 33.2% of adult and adolescent patients treated with lebrikizumab reached the Investigator's Global Assessment (IGA) 0/1 primary endpoint at week 16 versus 12.7% and 10.8% on placebo (both $P<0.001$), relieving pruritus and itch-related sleep disturbance. Lebrikizumab demonstrated consistent efficacy across diverse skin tones, an important consideration for equitable treatment access.

Lebrikizumab is administered every 2 weeks following a loading dose, with onset of action typically within 4 weeks. Meta-analyses suggest that dupilumab and lebrikizumab have similar efficacy and superiority to tralokinumab. Long-term safety and efficacy studies for lebrikizumab therapy for patients aged 6 months or older are currently under investigation.

Nemolizumab

Nemolizumab is a humanized monoclonal antibody that antagonizes the IL-31 receptor alpha chain (IL-31RA), thereby inhibiting the IL-31 cascade and reducing pruritus and inflammation. Nemolizumab was approved by the FDA in 2024 for moderate to severe atopic dermatitis in adolescents and adults aged 12 years and older, and previously received approval for prurigo nodularis in adults.

IL-31, a type 2 cytokine produced mainly by Th2 cells, induces pruritus by acting on sensory neurons in the skin. Nemolizumab rapidly reduces itch in AD patients, with significant improvement observed even after a single dose. Clinical data showed positive response among individuals treated with nemolizumab every 4 weeks in combination

with topicals, with the possibility to transition to every-8-week maintenance dosing after 16 weeks.

Nemolizumab's rapid onset of itch relief (within 1-2 weeks) distinguishes it from other biologics. However, paradoxical dermatitis flares have been observed in some patients treated with anti-IL31RA therapy, which may be explained by IL-31's dual role as both a pruritogenic and immunoregulatory factor that limits type 2 inflammatory responses. The most common adverse events are upper respiratory tract infection, allergic conjunctivitis, and headache.

Oral JAK Inhibitors

Oral Janus kinase (JAK) inhibitors represent a significant advancement in AD therapy, offering rapid onset of action and oral administration. JAK inhibitors work by blocking the JAK-STAT signaling pathway, which is crucial for multiple cytokines involved in AD pathogenesis. Although baricitinib (a JAK1/2 inhibitor) is approved for AD in Europe and Japan, upadacitinib and abrocitinib remain the only oral JAK inhibitors approved for AD in the United States for patients 12 years and older.

JAK inhibitors have shown significant improvements in AD severity markers, such as the Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA) scores, while providing profound beneficial effects on itching from the first week of treatment. Upadacitinib and abrocitinib have the highest short-term efficacy among the approved systemic therapies. In responders, biologics like dupilumab and tralokinumab catch up regarding long-term efficacy within continuous use.

Important safety considerations: The European Medicines Agency has released recommendations for the use of JAK inhibitors in patients at risk (cardiovascular and thromboembolic diseases, malignancies, former smoking, age ≥65 years). Laboratory tests are required before and during treatment. Certain limitations exist for patients at risk of thromboembolic incidents and those older than 65 years.

Upadacitinib

Upadacitinib, a selective JAK1 inhibitor, was approved by the FDA in 2021 for moderate to severe AD in adolescents and adults aged 12 years and older. Upadacitinib is administered orally once daily at doses of 15 mg or 30 mg. The onset of response is rapid, typically within the first 2 weeks.

Real-world effectiveness studies from multiple centers have demonstrated that both 15 mg and 30 mg dosages led to significant and sustained improvements in disease severity, pruritus, sleep disturbances, and quality of life, with 77.8% achieving EASI 75 and 39.2% achieving EASI 100 at week 52. Head-to-head phase 3 trials (Heads-Up study)

comparing upadacitinib 30 mg with dupilumab showed superior efficacy for upadacitinib in achieving rapid disease control.

Drug survival studies show favorable retention rates for upadacitinib, though lower than dupilumab. Upadacitinib is the most common second-line treatment after dupilumab and is frequently used as third-line therapy. Beyond AD, upadacitinib is approved for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis, ulcerative colitis, and Crohn's disease.

Common adverse events include upper respiratory tract infections, acne, increased creatine phosphokinase, headache, and laboratory abnormalities. Black box warnings include serious infections, increased mortality in patients 65 years and older, malignancies, major adverse cardiovascular events, and thrombosis. Close monitoring and careful patient selection are essential.

Abrocitinib

Abrocitinib, a selective JAK1 inhibitor, was approved by the FDA in 2022 for moderate to severe AD in adolescents and adults aged 12 years and older. Abrocitinib is administered orally once daily at doses of 100 mg or 200 mg. Like upadacitinib, abrocitinib offers rapid onset of action, typically within 1-2 weeks.

Head-to-head trials (JADE DARE) comparing abrocitinib 100 mg and 200 mg with dupilumab showed that the 200 mg dose achieved superior short-term efficacy. A 2024 label update allows flexible dosing, highlighting abrocitinib's potential in various inflammatory and autoimmune conditions. Publications have demonstrated patient phenotypes that have efficacious response to therapy (e.g., itch-dominant AD, regional disease) and offered insight on predicting longer-term response based on early response after only a few weeks of therapy.

Drug survival studies indicate moderate retention rates for abrocitinib. Common adverse events include nausea (particularly at initiation, often transient), upper respiratory infections, headache, acne, and herpes simplex infections. Similar to upadacitinib, abrocitinib carries black box warnings for serious infections, malignancies, major adverse cardiovascular events, and thrombosis.

Baricitinib

Baricitinib, a JAK1/2 inhibitor, was approved in Europe in 2020 for AD but is not approved for AD in the United States. Baricitinib is approved for rheumatoid arthritis, juvenile idiopathic arthritis, and alopecia areata in multiple regions. Drug survival studies show that baricitinib has the lowest survival rate among available targeted systemic therapies for AD, likely reflecting efficacy and tolerability differences.

Traditional Systemic Immunomodulatory Agents

A broad set of systemic immunomodulatory agents have been used for severe AD refractory to topical therapies. However, with the advent of targeted biologics and JAK inhibitors, the role of traditional systemic immunosuppressants has diminished. Systemic glucocorticoids such as oral prednisone are highly immunosuppressive but generally avoided in the treatment of chronic AD because of systemic toxicities and high relapse rates upon discontinuation. A 2025 position paper recommends minimizing systemic corticosteroid use in AD due to safety concerns.

Cyclosporin A is a potent immunosuppressive that works by inhibiting calcineurin. Multiple studies have demonstrated that both children and adults with severe AD refractory to conventional treatment can benefit from short-term cyclosporine treatment. Various oral dosing regimens have been used, with 5 mg/kg generally showing success in short-term and long-term (1 year) use. Treatment with cyclosporine has been associated with reduced skin disease and improved quality of life. However, discontinuation generally results in rapid relapse. Possible side effects include elevated serum creatinine level, renal impairment, and hypertension.

Other traditional systemic therapies that have been used include methotrexate, azathioprine, and mycophenolate mofetil. These systemic agents all have significant risks of systemic toxicities, requiring careful monitoring and restricting their use. Given the superior efficacy and safety profiles of newer targeted therapies, traditional immunosuppressants are increasingly reserved for cases where targeted therapies are contraindicated, unavailable, or have failed.

Probiotics

Perinatal administration of the probiotic Lactobacillus rhamnosus strain GG has been shown to reduce the incidence of AD in at-risk children beyond infancy. Several different studies showed that in not only infants but also children up to 13 years of age, treatment with lactobacillus was beneficial in patients with AD and allergies. However, the evidence for probiotics remains mixed, and current guidelines do not universally recommend their use.

Phototherapy

Broadband UV-B, broadband UV-A, narrow-band UV-B (311 nm), UV-A-1 (340-400 nm), psoralen ultraviolet A-range (PUVA), and combined UV-A-B phototherapy are useful adjuncts in the treatment of AD. These therapies are well established, though

relapse can occur after cessation of treatment. Most patients experience improvement in symptoms as well as reduction in topical corticosteroid use.

The photoimmunologic effects of UV-A phototherapy with and without psoralen are presumably mediated through Langerhans cells and eosinophils, whereas UV-B's immunosuppressive effects occur through blocking of antigen-presenting Langerhans cells and altered keratinocyte cytokine production. Photochemotherapy with PUVA might be indicated in patients with severe, widespread AD. Short-term adverse effects with phototherapy might include erythema, burns, pruritus, and pigmentation. Long-term adverse effects include premature skin aging and cutaneous malignancies.

Future Perspective

The therapeutic landscape for AD has undergone remarkable transformation in recent years. Over 40 novel topical compounds are currently in Phase 3 clinical development, targeting various pathways including aryl hydrocarbon receptor (AhR), Janus kinase (JAK) receptors, TRPV1, and phosphodiesterase-4 (PDE4) inhibitors. Additionally, numerous systemic therapies are under investigation, including multispecific biologics targeting multiple cytokines simultaneously.

Future studies are needed to focus on strategies preventing the initial development of AD. Given the central role of TH2 cytokines and chemokines in the development of allergic skin inflammation, strategies directed at reducing TH2 responses and blocking the action of chemokines by antagonists of CCR3 and CCR4 will be important. Further studies are also needed to examine the potential role of IFN-gamma, IL-12, and IL-18 in restoring the shift toward a more balanced TH0 response with equal production of TH1 and TH2 cytokines.

Direct head-to-head trials are urgently needed to establish clear comparative efficacy and safety profiles between different biologics and JAK inhibitors. In parallel, the development and validation of biomarker-driven treatment algorithms are paramount to better delineate patient subgroups and inform personalized therapeutic strategies. Specifically, prospective validation is required to determine if baseline tissue/serum IL-13 levels can serve as a primary predictive marker for response to IL-13 inhibitors. Exploring other biomarkers linked to type 2 inflammation, such as IL-31, IL-33, serum thymus and activation-regulated chemokine (TARC), periostin, and dipeptidyl peptidase-4 (DPP-4), could aid in predicting differential responses.

Advancements in understanding AD pathogenesis have led to active development of new treatment strategies including topical bacteriotherapy (using beneficial Staphylococcus species to displace S. aureus), OX40/OX40L antagonists, and multispecific biologics.

Artificial intelligence and machine learning approaches are being explored to better predict treatment responses and identify optimal therapeutic strategies for individual patients.

There is a strong rationale for examining the effect of therapeutic agents capable of blocking the actions of IL-4 and IL-5. Anti-IL-5 antibody has been shown to block eosinophil infiltration in sensitized animals. It would be of interest to determine the clinical effects of blocking the action of IL-4 in patients with AD. The combination of several approaches will be needed to effectively interrupt the complex inflammatory cascades associated with allergic diseases including AD.

The trend is shifting away from corticosteroids towards advanced targeted therapies, with expert panels providing guidelines for transitioning to these newer options. As the treatment landscape evolves, ongoing research is essential to assess long-term safety and efficacy, and to develop predictive models that optimize treatment strategies, ultimately improving patient outcomes and quality of life.

Evidence-Based Medicine in AD

Diagnosis: Global Prevalence and Epidemiological Assessment

A massive systematic review and meta-analysis of 310 studies (25.5 million individuals) established current global diagnostic benchmarks. It found a point prevalence of 11.1% in children and 6.3% in adults. The study highlighted that diagnostic rates vary significantly based on the criteria used (clinical assessment vs. symptom-based questionnaires), reinforcing the need for standardized diagnostic tools like the EASI and SCORAD scores in clinical practice.
Evidence Grade: 1a (A)

Management: Topical Anti-Inflammatory Treatments for Eczema

Systematic review using standard Cochrane methodology with network meta-analysis. Included within-participant or between-participant randomized controlled trials of people of any age with clinical diagnosis of eczema. Evaluated well-characterized topical anti-inflammatory treatments. Data from almost 300 trials. Comprehensive network comparison of topical anti-inflammatory agents including topical corticosteroids, calcineurin inhibitors, PDE4 inhibitors, and JAK inhibitors. Trials were mostly industry-funded, evaluated short-term outcomes, and carried high risk of bias due to selective reporting.
Evidence Grade: 1a (A)

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Tables

Table 12.1 Peripheral Blood Findings in Atopic Dermatitis

- Increased IgE levels
- Eosinophilia
- Increased basophil spontaneous histamine release
- Decreased CD8 suppressor/cytotoxic number and function
- Increased expression of CD23 on mononuclear cells
- Chronic macrophage activation with increased secretion of GM-CSF, prostaglandin E2, and IL-10
- Expansion of IL-4 and IL-5 secreting TH2-type cells
- Decreased numbers of IFN-gamma secreting TH1-type cells
- Increased serum sIL-2 receptor levels
- Increased serum eosinophil cationic protein levels
- Increased soluble E-selectin levels
- Increased soluble vascular cell adhesion molecule-1 levels
- Increased soluble intercellular adhesion molecule-1 levels
- Increased serum CCL17/TARC (thymus and activation-regulated chemokine) levels - most reliable AD biomarker
- Increased serum lactate dehydrogenase (LDH) levels
- Increased serum IL-6, IL-8, and TNF-α levels

- Increased serum IL-13, IL-22, IL-31, and IL-33 levels
- Increased circulating Th22 cells (IL-22 secreting)
- Increased circulating Th17 cells (IL-17 secreting) - particularly in Asian and intrinsic AD
- Increased type 2 innate lymphoid cells (ILC2)
- Increased circulating CLA+ (cutaneous lymphocyte-associated antigen) T cells
- Increased neutrophil-to-lymphocyte ratio (NLR)
- Increased platelet-to-lymphocyte ratio (PLR)
- Increased serum periostin levels
- Increased serum squamous cell carcinoma antigen 2 (SCCA2)
- Increased serum CCL26/eotaxin-3
- Increased circulating tissue-resident memory T cell (TRM) precursors
- Detectable circulating cell-free mitochondrial DNA
- Increased serum IL-17A and IL-17C (in Asian and intrinsic AD phenotypes)

Table 12.2 Multifunctional Role for IgE in Atopic Dermatitis

- IgE-dependent late-phase skin reaction
- Allergen presentation by IgE-bearing Langerhans cells
- Allergen-induced activation of IgE-bearing macrophages
- IgE autoreactivity to human keratinocyte proteins (found in ~28% of severe AD patients)
- IgE autoantibodies targeting cytoplasmic and membrane-associated keratinocyte antigens
- IgE autoantibodies to specific autoantigens: Hom s 1-5, MnSOD, thioredoxin, α-enolase, others
- IgE autoreactivity associated with disease severity and chronicity
- IgE autoreactivity more prevalent in AD with Type-2 comorbidities (16.4%) vs solely AD (9.6%)
- IgE autoreactivity associated with younger age at presentation
- IgE autoreactivity associated with atopic march progression
- IgE autoreactivity correlates with higher total serum IgE levels

Mechanisms of IgE-mediated pathology:

- IgE-autoantigen complexes promote facilitated antigen presentation
- IgE-mediated activation of mast cells and basophils at skin sites
- IgE-galectin 3 interactions contributing to chronic inflammation
- IgE-mediated skewing toward Type 2 immunity
- IgE-induced chronic skin barrier dysfunction
- IgE autoantibodies may contribute to development of autoimmune comorbidities

Environmental factors affecting IgE autoreactivity:

- Birth between January and June increases risk
- Cesarean section delivery increases risk
- Diversity of domestic pets influences development

Table 12.3 Factors Contributing to the Development of TH2 and Other T Helper Cell Subsets in Atopic Dermatitis

Classic TH2-promoting factors:

- Genetic background (e.g., IL-4 promoter polymorphism, filaggrin mutations)
- Cytokine milieu in which antigen presentation takes place (i.e., IL-4, IL-13)
- Antigen-presenting cell characteristics (e.g., Langerhans cells, dendritic cell subsets)
- Nature of antigen (e.g., allergens vs parasites)
- T/B cell costimulatory signals (i.e., CD28/B7.2 (CD86) interactions)
- Pharmacologic factors (i.e., prostaglandin E2, cAMP phosphodiesterase activity)

Innate immune activation and alarmin signaling:

- Skin barrier damage leading to keratinocyte stress
- Release of alarmins from damaged keratinocytes (TSLP, IL-25, IL-33)
- TSLP-mediated maturation and activation of Langerhans cells
- IL-33-mediated activation of type 2 innate lymphoid cells (ILC2)
- IL-25 amplification of Type 2 responses
- ILC2 production of IL-5 and IL-13 (T cell-independent mechanism)

Dendritic cell subset differentiation:

- Langerin+ (CD207+) dermal dendritic cells - rapid antigen presentation
- CD207+CD103+ dendritic cells vs CD207+CD103- dendritic cells
- CD207-CD11b+ dendritic cells
- TSLP-induced generation of inflammatory Langerin+ dendritic cells

Age-related factors:

- Pediatric AD: predominant Th2, increased Th9 and Th17 at disease onset
- Adolescent AD: increased Th2 and Th22 markers, elevated IL-16 and CXCL12
- Young adult AD (18-40 years): Th2, Th17, and Th1 pathways correlate with severity
- Older adult AD (≥61 years): Th2 and Th17 markers correlate with severity
- Adult AD: increased circulating Th22 cells compared to pediatric

Ethnic/racial genetic factors:

- Asian AD: enhanced Th17 and Th22 activation alongside Th2
- Asian AD: elevated IL-17A, IL-19, and IL-22 in lesional and non-lesional skin
- European AD: predominantly Th2 with less Th17/Th22 activation
- African American AD: variable Th1/Th17 patterns
- East African AD: significant barrier lipid gene defects

Disease phase and chronicity factors:

- Acute phase: dominant Th2 activation with ILC2 involvement
- Transition to chronic: progressive increase in Th22 and Th17 cells
- Chronic phase: Th1, Th17, and Th22 cells alongside persistent Th2
- Th22 (IL-22) and Th17 (IL-17) suppress filaggrin expression

- Chronic inflammation drives expansion of tissue-resident memory T cells

Skin barrier and microbial factors:

- Filaggrin mutation status (loss-of-function mutations)
- Epidermal barrier dysfunction allowing allergen penetration
- Staphylococcus aureus colonization and enterotoxins
- Skin microbiome dysbiosis
- Decreased microbial diversity
- Altered lipid metabolism (ceramides, fatty acids)

Intrinsic vs Extrinsic AD factors:

- Extrinsic AD (high IgE): strong Th2 with IgE-mediated mechanisms
- Intrinsic AD (normal IgE): greater Th17 and Th1 activation despite normal IgE
- Intrinsic AD shows comparable Th2 but higher Th17 vs extrinsic AD

OX40-OX40L costimulatory pathway:

The OX40-OX40L pathway is a crucial co-stimulatory signaling route in the immune system, primarily involving OX40 (a receptor on T-cells) and its ligand, OX40L (expressed on antigen-presenting cells), which promotes T-cell activation, survival, expansion, and differentiation, driving inflammatory responses and influencing immunity in conditions like atopic dermatitis.

- OX40 (CD134): A receptor found on activated T-cells (CD4+ and CD8+).
- OX40L (CD252, TNFSF4): A ligand (member of the TNF superfamily) expressed on antigen-presenting cells (like dendritic cells, B cells) and other cells.
- Alarmin-induced upregulation of OX40L on antigen-presenting cells
- OX40-OX40L interaction promotes Th2 differentiation in acute phase
- Sustained OX40-OX40L signaling drives Th1, Th17, Th22 proliferation in chronic phase

Environmental and epigenetic factors:

- Birth season (January-June) influences immune development
- Mode of delivery (cesarean section vs vaginal)
- Domestic pet diversity during early life
- Air pollution and climate factors
- Humidity and temperature effects on barrier function

Table 12.4 Defective Epidermal Barrier Findings in Atopic Dermatitis

Structural protein abnormalities:

- Reduced filaggrin expression and filaggrin breakdown products
- Decreased loricrin expression
- Decreased involucrin expression
- Impaired cornified envelope formation

- Altered keratinocyte terminal differentiation

Lipid barrier dysfunction:

- Decreased ceramide levels (particularly long-chain ceramides)
- Altered fatty acid composition
- Impaired lamellar lipid bilayer organization
- Reduced expression of lipid-metabolizing enzymes
- Increased transepidermal water loss (TEWL)

Tight junction abnormalities:

- Decreased claudin-1 expression
- Disrupted tight junction integrity
- Increased paracellular permeability

Antimicrobial peptide deficiency:

- Decreased β-defensin production
- Reduced cathelicidin (LL-37) levels
- Impaired antimicrobial barrier function
- Increased susceptibility to Staphylococcus aureus colonization

Protease imbalance:

- Increased serine protease activity (especially kallikreins)
- Dysregulated protease/antiprotease balance
- Premature desquamation
- Barrier disruption through corneodesmolysis

pH dysregulation:

- Elevated stratum corneum pH
- Impaired acidification
- Compromised enzymatic processes
- Altered microbial defense

Cytokine-mediated barrier suppression:

- IL-4 and IL-13 suppress filaggrin, loricrin, involucrin expression
- IL-22 inhibits keratinocyte terminal differentiation
- IL-17 disrupts epidermal homeostasis
- Th2 cytokines suppress antimicrobial peptide production

Table 12.5 AD Biomarkers by Clinical Utility

Disease activity monitoring:

- CCL17/TARC (most reliable, correlates with EASI/SCORAD)
- Lactate dehydrogenase (LDH)
- SCCA2 (squamous cell carcinoma antigen 2)
- CCL26/eotaxin-3
- Total IgE (variable utility)

- Eosinophil count

Endotype stratification:

- Th2 markers: IL-4, IL-13, CCL17, CCL22, periostin, IgE
- Th22 markers: IL-22, S100A proteins
- Th17 markers: IL-17A, IL-17C, IL-23
- Th1 markers: IFN-γ, CXCL9, CXCL10, CXCL11

Predictive biomarkers for therapy response:

- Baseline IgE levels (limited predictive value for dupilumab)
- IgE changes during treatment (may predict dupilumab efficacy)
- Baseline Th2 markers (may predict anti-IL-4/IL-13 response)
- Th17/Th22 markers (may predict better JAK inhibitor response)
- Eosinophil count (predictor for upadacitinib response)
- NLR and PLR ratios

Atopic march and comorbidity risk:

- IgE autoreactivity (associated with Type-2 comorbidities)
- Early life biomarkers: stratum corneum lipids and cytokines at 2 months
- Skin surface mRNA signatures at 1 month
- IL-33, IL-25, thymic stromal lymphopoietin (TSLP) levels

Minimally invasive biomarkers:

- Tape strip proteomics
- Tape strip transcriptomics
- Skin surface lipids
- Skin surface mRNA

Table 12.6 Alarmins and Innate Immune Mediators in Atopic Dermatitis

Thymic stromal lymphopoietin (TSLP):

- Released by damaged keratinocytes in response to barrier disruption
- Activates dendritic cells and Langerhans cells
- Induces Th2 cell differentiation
- Activates type 2 innate lymphoid cells (ILC2)
- Directly stimulates sensory neurons causing itch
- Elevated in both lesional and non-lesional AD skin
- Target of therapeutic monoclonal antibody (tezepelumab)

Interleukin-33 (IL-33):

- Nuclear alarmin released upon keratinocyte damage
- Potent activator of ILC2 cells
- Induces IL-5 and IL-13 production from ILC2
- Drives itch through IL-31 induction
- Amplifies Type 2 inflammation

- Present in subclinical inflammation in non-lesional skin

Interleukin-25 (IL-25, IL-17E):

- Epithelial-derived cytokine
- Activates ILC2 and Th2 cells
- Synergizes with TSLP and IL-33
- Amplifies Type 2 immune responses
- Contributes to barrier dysfunction

Periostin:

- TSLP-induced protein produced by keratinocytes
- Promotes Th2 inflammation
- Facilitates eosinophil recruitment
- Serum levels correlate with disease severity
- Biomarker for Type 2 inflammation

Other alarmins and damage signals:

- IL-1α and IL-1β from keratinocytes
- High-mobility group box 1 (HMGB1)
- S100A proteins (S100A8/A9)
  S100A8 and S100A9 are small, calcium-binding proteins belonging to the S100 family, which often function as a heterodimer complex known as calprotectin (also referred to as MRP8/MRP14, calgranulin A/B, or myeloid-related protein 8/14). They are crucial mediators of innate immunity, acting as pro-inflammatory alarmins that are highly expressed in neutrophils and monocytes, especially during acute and chronic inflammation.

- ATP and uric acid
- Heat shock proteins

Table 12.7 Itch Mediators in Atopic Dermatitis

Cytokine-mediated itch:

- IL-31 (primary pruritogenic cytokine, acts on sensory neurons)
- IL-4 and IL-13 (non-histaminergic neuronal itch transmission)
- TSLP (direct neuronal activation)
- Periostin (promotes itch-scratch cycle)

Cellular sources of itch mediators:

- Th2 cells: IL-31, IL-4, IL-13
- Group 2 Innate Lymphoid Cells **(**ILC2 cells): IL-5, IL-13
- Mast cells: histamine, tryptase, cytokines
- Eosinophils: eosinophil cationic protein
- Keratinocytes: TSLP, IL-33
- Basophils: histamine, IL-4

Neuronal mechanisms:

- TRP (transient receptor potential) sensory neuron activation
- TRPV1 and TRPA1 channels
  TRPV1 and TRPA1 are crucial non-selective cation channels in sensory neurons, detecting noxious stimuli like heat (TRPV1) and irritants (TRPA1), playing key roles in pain, inflammation, and reflex responses, often co-expressed and interacting to modulate sensation, influencing areas from airways to the gut and even heart, responding to chemical triggers like capsaicin (TRPV1) and mustard oil/AITC (TRPA1) alongside temperature and inflammatory mediators.

- Non-histaminergic itch pathways (predominant in AD)
- Neurokinin-1 (NK1) receptor signaling
- IL-31 receptor A (IL-31RA) on sensory neurons

Neutrophil-mediated itch:

- Skin-infiltrating neutrophils trigger itch
- CXCL10-dependent activation of CXCR3 on sensory neurons
- Neutrophil recruitment in acute flares

Itch-scratch amplification cycle:

- Scratching damages keratinocytes
- Release of TSLP and IL-33
- Further activation of Type 2 inflammation
- Periostin production perpetuates cycle

Therapeutic targets for itch:

- IL-31 receptor (nemolizumab)
- JAK/STAT pathway (abrocitinib, upadacitinib, baricitinib)
- IL-4/IL-13 pathway (dupilumab, tralokinumab)
- Histamine H4 receptor
- NK1 receptor antagonists
  NK1 receptor antagonists are a class of drugs, like aprepitant, that block Substance P from binding to Neurokinin-1 receptors, primarily used to prevent severe nausea and vomiting (CINV) caused by chemotherapy, offering relief in both acute and delayed phases, often combined with other antiemetics for enhanced effect. They work by targeting the brain's vomiting centers and show promise for other conditions like depression, anxiety, and inflammatory disorders, though their main use remains antiemetic.

- KOR agonists
  κ-opioid receptor agonists (KOR agonists) are compounds that activate κ-opioid receptors, providing potent analgesia for conditions like visceral pain, but have historically caused side effects such as sedation, dysphoria, and depression,

leading to current research focused on developing peripherally selective KOR agonists that avoid these central nervous system issues for safer pain management. While no KOR agonists are widely used clinically in the West, compounds like Nalfurafine (TRK-820) have shown promise for itch relief, highlighting their potential as safer alternatives to traditional μ-opioid agonists like morphine.

Table 12.8 Ethnic and Age-Related AD Endotypes

Asian AD phenotype:

- Strong Th2 component maintained
- Enhanced Th17 activation (elevated IL-17A, IL-17F)
- Increased Th22 activation (elevated IL-22, IL-19)
- Greater epidermal hyperplasia and Ki67 expression
  Ki-67 expression is an index indicating the rate of cell proliferation (proliferative capacity) and refers to the expression level of a nuclear protein (MKI67 gene product) that appears when cells divide. A high Ki-67 expression rate in cancer cells indicates rapid proliferation and higher malignancy. It is used as an important marker for prognosis prediction and treatment planning, particularly in cases of breast cancer.

- More lichenification in chronic lesions
- Higher IL-17 skin infiltration despite similar serum levels
- Dyskeratosis more common

European/Caucasian AD phenotype:

- Predominantly Th2-driven
- Lower Th17/Th22 activation compared to Asian
- More prominent acute eczematous changes
- Less epidermal thickening in chronic disease

African American AD phenotype:

- Variable Th1/Th17 patterns
- Greater barrier lipid deficiency
- Higher prevalence (19.3% in children)
- Distinct clinical morphology (follicular accentuation)

East African AD phenotype:

- Significant barrier lipid gene defects
- Most pronounced decrease in barrier lipid expression
- Distinct immunologic profile

Pediatric AD (infancy to early childhood):

- Predominant Th2 inflammation
- Increased Th9 activation at disease onset
- Elevated Th17 activation early
- ILC2 prominence
- Strong alarmin signature (TSLP, IL-33, IL-25)
- Acute eczematous morphology predominates

Adolescent AD (12-17 years):

- Increased Th2 and Th22 markers
- Elevated IL-16 and CXCL12 expression
- Transition toward chronic patterns
- Mixed acute and chronic lesions

Young adult AD (18-40 years):

- Th2, Th17, and Th1 pathways all correlate with severity
- Balanced multi-axis inflammation
- Variable clinical presentations

Middle-aged and older AD (≥41 years):

- Disease severity correlates more with Th17 markers
- Age ≥61 years: Th2 pathway still significantly correlates with severity
- Later-onset AD (adult-onset) shows more Th1/Th17 activation
- Greater chronicity and lichenification

Intrinsic AD (normal/low IgE):

- Comparable Th2 to extrinsic AD
- Significantly higher Th17 activation
- Enhanced IL-17 expression
- Normal or low total IgE (<200 IU/mL)
- 10-45% of AD cases depending on population
- More common in adults

Extrinsic AD (high IgE):

- Strong Th2 dominance
- IgE-mediated mechanisms prominent
- High total IgE (>200 IU/mL)
- Greater association with other atopic diseases
- 55-90% of AD cases
- More common in children

Table 12.9: Evidence for Role of Staphylococcal Superantigens in Atopic Dermatitis

S. aureus colonization and superantigen production:

- Majority of Staphylococcus aureus isolates secrete superantigens
- Majority of patients with AD produce IgE antibodies to superantigens

- AD severity correlates with presence of IgE antibodies to superantigens
- Superantigens augment allergen-induced skin inflammation
- Superantigens induce dermatitis on application to skin by patch testing
- Chronic eczema develops in patients recovering from toxic shock syndrome
- Superantigens induce the cutaneous lymphocyte antigen skin-homing receptor on T cells
- Peripheral blood mononuclear cells from AD, as compared with normal control subjects, have higher proliferative responses to superantigens
- Superantigens induce corticosteroid resistance
- Treatment with a combination of anti-staphylococcal antibiotics and topical corticosteroids is more effective than using either medication alone

Colonization patterns and genetics:

- S. aureus colonizes 30-100% of AD patients vs 5% of healthy individuals
- Two-thirds of S. aureus isolates from lesional skin encode superantigens vs one-third from nasal isolates
- Heterogeneous S. aureus population with varying superantigen gene profiles (sea, seb, sec, sed, see, tsst-1, exfoliative toxins)
- Most common superantigen genes in AD patients: SEC and SEA (varies by population)
- CC7 clonal complex shows increased prevalence in some AD populations
- Different superantigen distribution patterns between adult and pediatric AD patients
- Nasal mucosa serves as major reservoir for S. aureus strains (65% with nasal colonization also show skin colonization)
- Same toxins detected in matched nasal and skin isolates from individual patients

Virulence factors beyond superantigens:

- Alpha-toxin (α-hemolysin) induces keratinocyte cytotoxicity in AD skin
- Keratinocytes in AD more susceptible to α-toxin due to reduced filaggrin and sphingomyelinase expression
- Protein A activates tumor necrosis factor receptor-1 on keratinocytes, inducing TSLP and IL-8
- Lipoproteins activate toll-like receptor 2 on keratinocytes
- Phenol-soluble modulins (PSMs) contribute to inflammation
- Lipoteichoic acid (LTA) acts as TLR-2 agonist
- Clumping factor B enhances adherence
- Proteases induce increased serine protease activity in keratinocytes, disrupting skin barrier

Mechanisms of S. aureus pathogenicity:

- S. aureus penetration into dermis correlates with increased IL-4, IL-13, IL-17, IL-22, TSLP expression
- Decreased LL-37 (cathelicidin) antimicrobial peptide expression facilitates colonization
- Altered lipid composition in stratum corneum promotes S. aureus adhesion
- Exposed extracellular matrix adhesins in damaged AD skin

- S. aureus exacerbates Th2/Th17 polarization
- Superantigens activate polyclonal T cells, causing T cell-mediated inflammation by binding TCR and MHC class II
- Greater than 80% of S. aureus from AD patients show highly abnormal and complex superantigen patterns

Impact on disease course:

- S. aureus colonization both cause and consequence of allergic skin inflammation
- Colonization density correlates with disease severity on both affected and unaffected skin
- S. aureus contributes to microbial dysbiosis
- May promote allergen sensitization and food allergy development
- Contributes to atopic march progression
- Increased risk of invasive infections (impetigo, cellulitis, abscesses, bacteremia, sepsis)
- Higher frequency of methicillin-resistant S. aureus (MRSA) in AD patients than healthy population

Controversial findings:

- Presence or absence of superantigen alone may not affect clinical severity of impetiginized AD lesions in some studies
- Levels of LTA, SPA, and pro-inflammatory cytokines similar between superantigen-expressing vs non-expressing S. aureus-infected AD lesions in some studies
- Suggests superantigens may not play primary role in clinical worsening of impetiginized AD (conflicting evidence)

Therapeutic implications:

- Bleach baths (dilute sodium hypochlorite) show antimicrobial and anti-inflammatory effects
- Combination anti-staphylococcal antibiotics plus topical corticosteroids more effective than either alone
- Topical antimicrobial peptide omiganan reduces S. aureus load but limited clinical efficacy as monotherapy
- No S. aureus vaccine currently authorized, but strategies targeting toxins in development
- Topical probiotics show promise against S. aureus
- Topical niclosamide (ATx201) reduces S. aureus colonization and increases Shannon diversity
- Antimicrobial photodynamic inactivation (aPDI) effectively inactivates heterogeneous S. aureus population in vitro

Table 12.10: Optimal Bathing and Moisturizing for Atopic Dermatitis (Updated 2025)

Bathing Recommendations

Frequency and duration:

- Daily to every other day bathing recommended (most common guideline)
- Short duration: 5-10 minutes recommended (updated from previous 20 minutes)
- Lukewarm water temperature (avoid hot water)
- Longer baths (up to 20 minutes) may be considered for severe flaring or very dry skin
- Wet compresses remain option if bathing is painful or for nighttime itch control

Bathing technique:

- Use gentle, fragrance-free, hypoallergenic, neutral pH cleansers or non-soap cleansers
- Limited use of soap (minimize to reduce skin irritation)
- Avoid products with added fragrance, dyes, or essential oils
- Avoid washcloths, rubbing, scrubbing
- Pat dry partially with towel—do not rub
- Leave some water on skin before moisturizer application

Bathing additives:

- Bleach baths (dilute sodium hypochlorite): Recommended as adjuvant therapy for moderate-to-severe AD
    - Antimicrobial and direct anti-inflammatory effects
    - Limited to 10 minutes per bath
    - Can be performed 2-3 times per week
    - Shows minor improvement in AD severity
- Emollient bath additives: Evidence does NOT support efficacy in reducing AD severity (updated recommendation)
- Oatmeal baths: May provide symptomatic relief (limited evidence)

Moisturizing Recommendations:

Timing and frequency:

- Apply moisturizer immediately after bathing (within 3 minutes) while skin still damp
- This improves epidermal barrier and decreases transepidermal water loss (TEWL)
- Apply at least once daily, often multiple times per day
- Titrate to symptomatic benefit
- Continue daily moisturizer on days when topical anti-inflammatory drugs are not used

Moisturizer selection:

- Over-the-counter, bland (fragrance-free and hypoallergenic), occlusive moisturizers preferred
- Ointments: Most occlusive, strong emollient effect, but greasy texture
- Creams: Less occlusive but more tolerable for patients
- Lotions: Generally avoided (less effective)
- No significant difference in efficacy between different moisturizer types—best

moisturizer is one consistently used
- Avoid fragrance, dyes, essential oils, and potential contact allergens

Application technique:

- Apply liberally to entire body skin surface
- Apply to "other areas" (non-inflamed skin) after applying topical anti-inflammatory medications to red, itchy areas
- Do NOT mix topical anti-inflammatory medications with emollients unless specifically instructed (dilutes potency)
- Repeat as often as necessary to keep skin soft throughout the day

Evidence for moisturizer benefits:

- Reduces AD severity and flare frequency
- Decreases topical prescription medication use
- Increases time between flares
- May be sufficient to control mild AD
- Improves skin barrier function

Important updates on moisturizer use:

- Moisturizers do NOT prevent AD development (updated evidence from BEEP and PreventADALL trials 2020-2024)
- Previous studies suggesting preventive benefit have been contradicted by large RCTs
- Prophylactic emollients show no statistically significant reduction in AD incidence
- In preterm infants, petrolatum-based ointments associated with increased candidemia and coagulase-negative Staphylococcus infections

Topical Anti-inflammatory Application:

Application sequence:

- Within 3 minutes after bathing, while water still on skin:
    1. Apply topical anti-inflammatory (corticosteroid, calcineurin inhibitor, PDE-4 inhibitor, JAK inhibitor) to red, itchy, inflamed areas
    2. Apply moisturizer to all other areas
- Apply topical anti-inflammatories once to twice daily to active eczema patches
- Do not mix with moisturizers unless instructed

Proactive therapy:

- Regular intermittent application of topical anti-inflammatory drugs can suppress inflammation flares
- Apply at earliest signs of local flare to prevent symptom progression
- Continue even when skin appears clear in areas prone to recurrent flares
- Reduces frequency of AD flares

Additional Skin Care Measures:

Trigger avoidance:

- Low humidity environments
- Harsh soaps or detergents
- Contact allergens (more common in AD patients)
- Skin irritants
- Temperature extremes
- Wool and synthetic fabrics (prefer soft cotton)

Educational components:

- Provide written action plan for AD management
- Education on disease nature and treatment
- Ensure proper medication use and adherence
- Address psychological impact and quality of life

Wet wrap therapy:

- Conditionally recommended by AAD 2023 guidelines
- Utilizes wet bandages to hydrate and soothe skin
- Provides barrier against scratching
- Helps decrease redness and inflammation
- Can reduce bacteria on skin
- Used for moderate-to-severe AD during flares

Important Physiological Considerations:

Hydration dynamics:

- Bathing without moisturizer decreases skin hydration below baseline
- Bathing followed by immediate moisturizer application increases hydration initially, but effect decreases over time
- At 90 minutes post-application, hydration may not be significantly greater than baseline
- Emollient application alone provides greatest average hydration benefit for AD patients
- AD patients retain moisture less well than individuals with normal skin
- No statistical difference between immediate vs delayed (within 3 minutes) moisturization

Barrier dysfunction in AD:

- Decreased filaggrin and filaggrin degradation products
- Abnormal ceramide content in stratum corneum
- Impaired moisture retention capacity
- Enhanced transepidermal water loss (TEWL)
- TEWL correlates with clinical severity

Table 12.11 Topical Medications such as Corticosteroids and Non-Corticosteroid Agents for AD

Brand Name	Generic Name	Class / Notes
TOPICAL CORTICOSTEROIDS		
CLASS 1 – SUPERPOTENT (Very High Potency)		
Clobex	Clobetasol propionate 0.05%	Lotion, Shampoo, Spray
Temovate	Clobetasol propionate 0.05%	Cream, Ointment, Solution, Gel
Olux	Clobetasol propionate 0.05%	Foam
Diprolene	Betamethasone dipropionate 0.05%	Gel, Ointment
Ultravate	Halobetasol propionate 0.05%	Cream, Ointment, Lotion
Psorcon	Diflorasone diacetate 0.05%	Ointment
Bryhali	Halobetasol propionate 0.01%	Lotion (FDA 2018)
CLASS 2 – POTENT (High Potency)		
Diprolene AF	Betamethasone dipropionate 0.05%	Cream
Elocon	Mometasone furoate 0.1%	Ointment
Halog	Halcinonide 0.1%	Cream, Ointment
Lidex	Fluocinonide 0.05%	Cream, Gel, Ointment, Solution
Topicort	Desoximetasone 0.25%	Cream, Ointment
Topicort	Desoximetasone 0.05%	Gel
CLASS 3 – UPPER MID-STRENGTH		

Cutivate	Fluticasone propionate 0.005%	Ointment
Luxiq	Betamethasone valerate 0.12%	Foam
Topicort	Desoximetasone 0.05%	Cream
Kenalog	Triamcinolone acetonide 0.5%	Cream, Ointment
CLASS 4 – MID-STRENGTH (Medium Potency)		
Kenalog	Triamcinolone acetonide 0.1%	Cream, Ointment, Lotion
Elocon	Mometasone furoate 0.1%	Cream, Lotion
Derma-Smoothe/FS	Fluocinolone acetonide 0.01%	Oil
Westcort	Hydrocortisone valerate 0.2%	Cream, Ointment
Locoid	Hydrocortisone butyrate 0.1%	Cream, Ointment, Solution
CLASS 5 – LOWER MID-STRENGTH		
Cutivate	Fluticasone propionate 0.05%	Cream, Lotion
Dermatop	Prednicarbate 0.1%	Cream, Ointment
DesOwen	Desonide 0.05%	Ointment
CLASS 6 – MILD (Low Potency)		
DesOwen	Desonide 0.05%	Cream, Lotion, Gel
Verdeso	Desonide 0.05%	Foam
Aclovate	Alclometasone dipropionate 0.05%	Cream, Ointment
CLASS 7 – LEAST POTENT (Very Low Potency)		
OTC/Rx	Hydrocortisone 0.5%, 1%, 2.5%	Various formulations

NON-CORTICOSTEROID TOPICAL MEDICATIONS		
TOPICAL CALCINEURIN INHIBITORS (TCIs)		
Protopic	Tacrolimus 0.03%, 0.1%	BID; ≥2 yrs (0.03%), ≥16 yrs (0.1%)
Elidel	Pimecrolimus 1%	BID; ≥2 years
PHOSPHODIESTERASE-4 (PDE4) INHIBITORS		
Eucrisa	Crisaborole 2%	BID; ≥3 months
Zoryve	Roflumilast 0.15% cream	QD; ≥6 years (FDA July 2024)
Zoryve	Roflumilast 0.05% cream	QD; 2-5 years (Expected 2025)
TOPICAL JAK (JANUS KINASE) INHIBITORS		
Opzelura	Ruxolitinib 1.5%	BID; ≥2 yrs (FDA Sept 2024)
Anzupgo	Delgocitinib 0.25%, 0.5%	BID; Hand eczema only (FDA July 2024)
ARYL HYDROCARBON RECEPTOR (AhR) AGONIST		
Vtama	Tapinarof 1%	QD; ≥2 years (FDA Dec 2024)

Topical Corticosteroids:

• **Vehicle matters:** Ointments > Creams > Lotions for same steroid

• **Body site:** Use Class 6-7 for face/groin/axillae; Class 1-2 for palms/soles/thick plaques

• **Duration:** Class 1-2 max 2-4 weeks; Class 3-5 up to 12 weeks with monitoring

• **Proactive therapy:** Apply to previously affected areas 2x/week to prevent flares

Non-Corticosteroid Topicals:

• **Calcineurin Inhibitors:** No skin atrophy; ideal for face/groin; initial burning usually resolves

• **PDE4 Inhibitors:** Once-daily options (roflumilast); mild-moderate efficacy

• **JAK Inhibitors:** Rapid itch relief; short-term/non-continuous use; avoid with biologics

• **Tapinarof:** Newest option (Dec 2024); once-daily; works all ages ≥2 years

Recent FDA Approvals (2024-2025):

• **July 2024:** Roflumilast 0.15% cream, Delgocitinib

• **September 2024:** Ruxolitinib expanded to ages ≥2 years

• **December 2024:** Tapinarof for atopic dermatitis