Review article

Endotypes of atopic dermatitis

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Atopic dermatitis (AD) is a chronic, heterogeneous skin condition driven by a combination of genetic, immune, and environmental factors. The original classification into extrinsic and intrinsic endotypes has proven to be too simplistic. Recent research into the varied immune profiles and molecular signatures of AD has revealed distinct endotypes—that is, subtypes defined by specific biological processes rather than visible symptoms alone. These endotypes encompass classifications that are based on immune pathways, including T_H2 dominant, T_H1, T_H17/T_H22-driven responses, genetic factors, and microbial interactions. Recognizing these endotypes has become essential for advancing personalized treatments because each subtype responds differently to immune-modulating therapies. Current treatment options, such as moisturizers, immunosuppressants, and biologics, show varied efficacy across AD endotypes, underscoring the need for more precise, endotype-specific approaches. Emerging molecular profiling technologies offer promising avenues to identify distinct biomarkers, refining AD classification and paving the way for more targeted treatments and improved patient outcomes. (J Allergy Clin Immunol 2025;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, endotypes, molecular profiling, personalized medicine, biomarkers*

Abbreviations used

AD:	Atopic dermatitis
AhR:	Aryl-hydrocarbon receptor
CCL:	Chemokine (C-C motif) ligand
CCR4:	C-C chemokine receptor type 4
CLA:	Cutaneous lymphocyte-associated antigen
EASI:	Eczema Area and Severity Index
FLG:	Filaggrin
JAK:	Janus kinase
miRNA:	MicroRNA
PDE4:	Phosphodiesterase 4
SCORAD:	SCORing Atopic Dermatitis
STAT:	Signal transducer and activator of transcription
TARC:	Thymus and activation-regulated chemokine
TEWL:	Transepidermal water loss
TSLP:	Thymic stromal lymphopoietin

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic inflammatory skin disease, affecting 10-20% of children[1,2] and 2-10% of adults,[2,3] with prevalence varying by region and population.[4] Characterized by dry, itchy, and inflamed skin, AD involves cycles of flare-ups and remissions triggered by stress, infections, weather changes, and allergens. Although it typically begins in infancy, AD often persists into adulthood, necessitating lifelong management that causes substantial financial[5] and mental impacts on individuals and society.[6,7]

The causes of AD are complex, involving genetic, immune, systemic, and environmental factors. Many patients have a family history of allergies, such as asthma or rhinitis.[8] Genetic mutations and environmental factors contribute to immune dysfunction and weakened skin barriers, making the skin more vulnerable to irritation and infection.[9] AD skin often lacks essential lipids, resulting in moisture loss, inflammation, and itch, with chronic scratching leading to skin thickening and lichenification.

The immune response in AD involves T_H2 cell activation, IgE production, and T_H2-type cytokines like IL-4, IL-5, and IL-13, all of which exacerbate inflammation and barrier dysfunction in atopic individuals.[10] While acute AD flares are largely T_H2 driven, chronic AD includes T_H1, T_H17, and T_H22 responses.[10] Reduced antimicrobial peptides like cathelicidins and defensins further compromise AD skin, increasing susceptibility to infections, particularly with *Staphylococcus aureus,* which colonizes up to 90% of patients and exacerbates severity.[11] Treatment options include moisturizers, anti-inflammatory agents (eg, corticosteroids, calcineurin inhibitors, phosphodiesterase 4 [PDE4] inhibitors), phototherapy, immunomodulators, and biologics.[12,13]

The heterogeneity of AD, including its varied clinical features and underlying mechanisms, has led to the identification of distinct endotypes, or subgroups, defined by specific biological processes. Recent advances in molecular profiling and immune characterization have provided a more detailed understanding of these endotypes, revealing significant variability across ethnic groups, age categories, and disease severity. This review builds on prior work by integrating emerging insights from high-throughput omics technologies, such as genomics, transcriptomics, and microbiome research, to refine endotype classifications. Additionally, we highlight the interplay between immune mechanisms, microbial dynamics, and environmental factors, offering a comprehensive framework for understanding AD endotypes.

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By synthesizing these findings, this review uniquely bridges the latest scientific advancements with practical implications for precision medicine, emphasizing novel therapeutic approaches tailored to specific AD endotypes. This integrated perspective aims to inform more effective and personalized treatments, addressing gaps in current AD management.

DEFINING AD ENDOTYPES

Understanding patients' immune profiles, genetic backgrounds, disease onset, and environmental factors allows for a more precise categorization of AD endotypes. These endotypes are crucial to shifting from a one-size-fits-all model to a personalized approach, with therapies tailored to individual immune, genetic, and molecular profiles.[14]

Extrinsic and intrinsic AD subtypes

AD is commonly classified into two major subtypes according to serum IgE level: extrinsic (elevated IgE) and intrinsic (normal IgE) (Fig 1, *A*). Approximately 80% of AD cases are extrinsic, often associated with protein allergies and early onset, while 20% are intrinsic.[15] Extrinsic AD is linked to impaired skin barrier function, higher transepidermal water loss (TEWL), and filaggrin *(FLG)* gene mutations, which increase the risk of eczema and food allergies.[16,17] It is characterized by a T_H2-dominant immune response and elevated eosinophils.[18] Intrinsic AD, more common in women with later onset, is often more severe and not typically related to barrier dysfunction. Although once called *nonallergic AD,* intrinsic AD can involve sensitization to metals like nickel. While both subtypes show T_H2 signaling, intrinsic AD also exhibits stronger T_H1 and T_H17 activation, with higher levels of IFN-γ–producing T_H1 cells in the blood.[19]

Concept of endotypes

The original classification into extrinsic and intrinsic endotypes[20] has proven overly simplistic. More detailed subendotypes have since been described on the basis of pathophysiologic mechanisms, including immune response endotypes (T_H2, T_H17/T_H22, or T_H1),[21] genetic endotypes (*FLG* or other mutations), age at disease onset (pediatric- or adult-onset AD), ethnic and geographic variations (Asian vs European), disease severity endotypes (mild, moderate, or severe), or infectious endotypes (eg, *S aureus* colonization) (Fig 1, *B* and *C*). Recent advancements in high-throughput technologies, particularly omics[22] (genomics, transcriptomics,[23-26] proteomics,[23,26-28] and metabolomics[28]), are revolutionizing medicine by incorporating big data analysis, including bioinformatics, systems biology, and synthetic biology, to improve patient clustering, endotype identification, and treatment optimization.[29] AD endotypes can be identified by serum protein biomarker analyses, while gene expression profiling provides deeper insights into dominant immune pathways and associated gene signatures.[30]

IMMUNE PATHWAYS AND CYTOKINE NETWORKS IN AD ENDOTYPES

AD pathogenesis is traditionally dominated by type 2 (T_H2) immune responses.[10] However, emerging evidence shows that AD cannot be confined to the T_H2 paradigm alone. Different endotypes of AD exhibit diverse cytokine profiles, engaging various T helper cell subsets, each contributing uniquely to disease severity, clinical manifestation, and treatment response. While *phenotypes* refer to observable clinical characteristics such as disease severity and skin barrier function, *endotypes* are defined by distinct molecular and immune mechanisms underlying these clinical features.

T_H2 dominance and classical endotypes

In most patients with AD, particularly those with early-onset and severe disease, or combined with food allergy and epidermal barrier dysfunction,[31] the immune response is dominated by T_H2 cells, which secrete cytokines such as IL-4, IL-13, and IL-31.[10] These cytokines impair skin barrier function by downregulating filaggrin expression and enhancing IgE production, which fuels allergic sensitization.[30,32] Elevated IL-13 levels are strongly associated with skin barrier dysfunction and inflammation, making it a key therapeutic target for biologics like dupilumab[33-38] (binds IL-4Ra, inhibiting IL4R signaling induced by both IL-4 and IL-13) and tralokinumab[24,39-42] (neutralizes IL-13 by blocking its binding to the receptor). T_H2-dominant endotypes are typically associated with increased eosinophilia and pruritus—hallmarks of classical AD.[43,44] The identification of these endotypes remains an ongoing area of research and is not yet fully realized. However, advancements in biomarker and cytokine profiling have enabled more precise classification of endotypes, allowing clinicians to tailor therapies more effectively, thereby reducing disease severity and improving patient outcomes.

T_H22 and skin remodeling

T_H22 cells drive epidermal hyperplasia and disrupt the skin barrier, contributing to the chronicity of AD.[45-47] The IL-22–high endotype is prominent in patients with chronic AD lesions and is associated with significant epidermal thickening and alterations in the skin microbiota.[46-48] While tissue remodeling in the classical sense is well established in asthma, its role in AD remains less defined. Unlike the irreversible tissue damage seen in asthma, epidermal thickening in AD is primarily due to reversible acanthosis driven by IL-22. This cytokine contributes to keratinocyte proliferation, making it a potential target for therapies aimed at modulating skin changes associated with chronic disease. Although research on IL-22 modulation is ongoing, further studies are needed to determine whether this represents a distinct inflammatory profile or is primarily a feature of chronic disease progression.

T_H1, T_H17 pathways, and geographic variations

While T_H2 cells dominate most AD cases, T_H1 and T_H17 cells are participating in nonclassical phenotypes.[49,50] The T_H17 axis contributes to neutrophilic inflammation and is associated with psoriasiform AD phenotypes, characterized by epidermal hyperplasia and barrier dysfunction.[51,52]

The European American AD extrinsic subtype is primarily driven by strong T_H2/T_H22 signaling with minimal T_H1 or T_H17 involvement.[14] Conversely, Asian AD subtypes show significant T_H17 activity and greater epidermal thickness, resembling psoriasiform changes such as hyperplasia, parakeratosis, and focal hypogranulosis.[50,52,53] Despite these inflammatory changes,

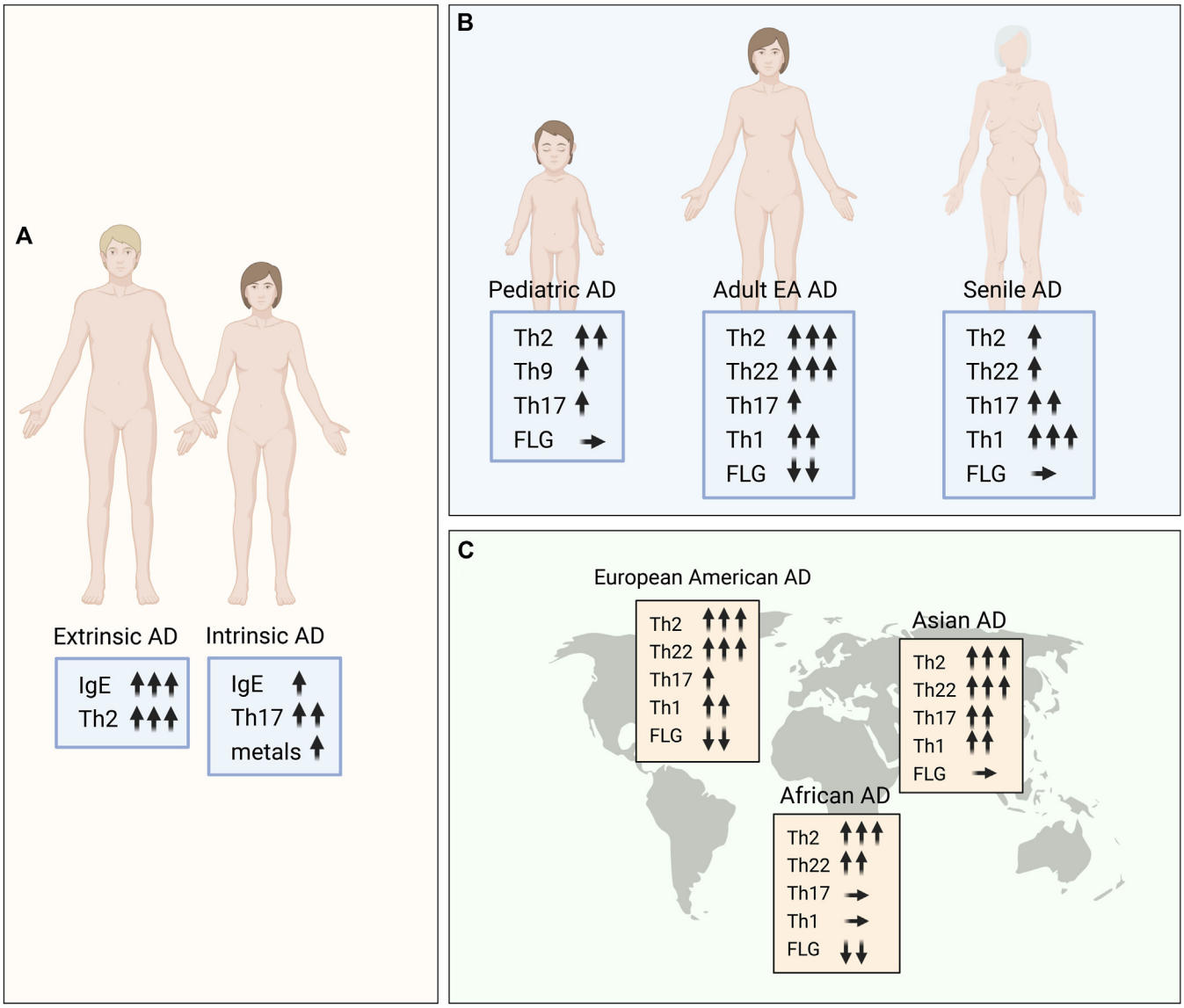

FIG 1. Classification of AD subtypes. **(A)** Extrinsic AD is characterized by high IgE levels and strong T_H2 immune response; intrinsic AD involves increased T_H17 activity, lower IgE levels, and higher prevalence of sensitization to metals. **(B)** Pediatric AD shows strong T_H2 response along with T_H17 and T_H9 signaling, relatively weaker T_H1 response, and expression of *FLG* similar to those in healthy individuals. Adult AD displays strong T_H2 and T_H22 response, moderate T_H17 response, and significantly lower *FLG* expression in skin. Senile AD features strong T_H1 and T_H17 response, moderate T_H22 and T_H2 activity, and little to no reduction in epidermal *FLG* expression. **(C)** For geographic variation in AD endotypes, AD in European American populations exhibits strong T_H2 and T_H22 response, low to moderate T_H17 and T_H1 response, and marked reduction in *FLG* expression. Asian AD also has strong T_H2 and T_H22 response, moderate T_H17 and T_H1 activity, but relatively preserved *FLG* expression. African American AD is characterized by pronounced T_H2 polarization, moderate T_H22 activity, significantly lower T_H17 and T_H1 response, and no substantial impact on *FLG* expression in epidermis.

epidermal barrier proteins are relatively well preserved in Asian AD, and T_H1 signaling is lower.[50] In African populations, AD is also characterized by strong T_H2/T_H22 immune responses, but with unique markers such as thymic stromal lymphopoietin (TSLP), IL-10, and chemokine C-C motif ligand (CCL) 13, alongside reduced innate immune signaling and lower T_H1/T_H17 responses. Elevated serum IgE levels reflect the heightened T_H2 response in African AD, though *FLG* loss-of-function mutations are rare in this population.[54] Understanding these regional and ethnic immune variations is crucial for developing more effective, population-specific treatments.

Data-driven analysis of endotypes in AD

Serum biomarker analysis identified 4 distinct clusters among adult AD patients, each defined by varying levels of T_H2 cytokines and differences in host defense–related gene expression, including IFN-β, CXCL9, and IL-1 family members IL-1α and

IL-1β.[55,56] A similar study in pediatric AD patients also identified 4 clusters, but only one overlapped with the adult subtypes, suggesting potential age-related differences in disease mechanisms.[57] Among these clusters, one was classified as the skin-homing–dominant cluster, characterized by elevated levels of apelin and key skin-homing markers, including PARC (pulmonary and activation-regulated chemokine)/CCL18, TARC/CCL17, and CTACK/CCL27. This cluster was associated with particularly severe and persistent AD.

In parallel, a blood transcriptome study classified AD patients according to eosinophil-associated gene expression levels. Despite molecular differences, clinical characteristics remained largely similar between the groups, and the disease of most patients, regardless of molecular endotype, responded at least partially to T_H2-targeted treatments.[58]

A skin transcriptome study further identified AD subtypes with distinct molecular signatures, including increased IL-1 family signaling (including IL-36A and IL-36G), keratinization-associated gene expression, epidermal differentiation, negative immune regulation, and B lymphocyte immune signaling. Among these, the subtype with heightened IL-1 family signaling was associated with the most severe disease and the highest levels of *S aureus* colonization.[59] Notably, because this study used an unsupervised, data-driven approach rather than focusing on preselected genes, it did not detect certain low-variance genes between clusters—such as *IL4R, TSLP, IL17A, FLG1, CLDN1, IL19,* and *IL22*—despite their known importance in AD pathophysiology.

GENETIC FACTORS DRIVING ENDOTYPE-SPECIFIC DISEASE MECHANISMS

Genetic predispositions

Genetic predispositions significantly influence AD endotypes, with variations in immune-regulatory and skin barrier genes affecting disease susceptibility and severity.[30,60,61] Twin studies show an approximate 75% heritability for AD, with *FLG* mutations identified as the strongest genetic risk factor, especially for early-onset, T_H2-dominant AD.[62-64] These mutations compromise skin barrier function, increasing permeability and allowing environmental allergens, irritants, and microbes to penetrate, which initiates an inflammatory response.[62,63]

Ethnic differences in genetic risk

The heterogeneity of AD is shaped by genetic differences across various ethnic groups. While *FLG* mutations are a well-established and widely replicated risk factor for AD,[65] only 10% to 40% of AD patients carry these mutations, and their prevalence varies significantly by ethnicity. Studies report that *FLG* mutations are present in 50% of European AD patients, 27% of Asian patients,[66] and just 5.8% of those with African ancestry.[67] Interestingly, among individuals of African descent, the *FLG2* gene is more strongly linked to AD risk.[68] Despite lower rates of *FLG* mutations in African populations, severe AD remains prevalent, suggesting that alternative genetic or environmental factors may contribute to disease onset and severity.[69,70] Moreover, some *FLG* variants also differ between European Americans and African Americans.[71]

Genetic variants and AD endotypes

Adult-onset AD is associated with genetic variations distinct from those linked to early-onset AD. The 4 most common *FLG* gene mutations, typically associated with early-onset AD (before age 8), are absent in cases of later-childhood AD (8-18 years) and adult-onset AD (after 18 years). Instead, mutations in the *CHI3L1* gene, which plays a key role in tissue injury, inflammation, and remodeling, have been associated with later-onset AD.[72,73]

Both innate and adaptive immune components are linked to AD, including mediators of the T_H2 pathway,[69] Toll-like receptors,[74] human β-defensin 1,[75] TSLP,[76,77] and the IL-1 family of cytokines.[78] Polymorphisms in IL-4 and IL-13,[79] as well as TSLP,[76] have been associated with AD. These cytokines, located within the T_H2 cytokine cluster on chromosome 5q31.1, contribute to the immune dysregulation observed in AD.[80-82] Additionally, single nucleotide polymorphisms in IL-12 cytokines, their receptors, and β-defensin 1 have been tied to increased AD risk in Korean populations.[83]

Rare genetic variants, such as loss-of-function mutations in *CARD14,* have been associated with severe AD, highlighting the role of less common genetic drivers in disease severity.[84] The role of genetic variation in shaping AD endotypes continues to be explored, with large-scale sequencing efforts, such as whole-exome and whole-genome sequencing, expected to uncover additional risk variants and help explain the missing heritability of AD.[69,84]

Genome-wide insights

Genome-wide association studies have identified previously over 30 loci associated with AD, many of which influence skin barrier development and immune response mechanisms.[69] For instance, variants in the chromosome 11q13.5 region and other loci involved in T-cell activation have been robustly linked to AD susceptibility across multiple populations.[69,70] These findings underscore the complexity of genetic contributions to AD and suggest that different genetic variants may influence distinct AD endotypes.[69,85,86]

In the latest and largest genome-wide association study for AD, 81 loci were identified in the European-only analysis, of which 29 were novel, along with 10 additional loci from the multiancestry analysis.[87] Many of these loci are enriched in DNase I hypersensitivity sites, especially in blood samples, highlighting the role of systemic immune regulation in AD. These sites mark active regions in the genome, and their analysis also revealed expression quantitative trait locus associations, linking these loci to gene expression variations. Furthermore, candidate genes at these loci are primarily involved in immune pathways related to atopic inflammation, underscoring the intricate genetic architecture of AD and offering potential drug repurposing opportunities.[87]

Using biobank data from the FinnGen study, the Estonian Biobank, and the UK Biobank, a large-scale meta-analysis involving nearly 800,000 participants identified 30 genetic loci associated with AD, including 5 novel loci.[86] Notably, missense mutations in *DSC1* (desmocollin 1) and *SERPINB7* (serpin family B member 7) were found to disrupt protein folding, weakening epidermal barrier integrity.[86] These findings emphasize the interplay between immune pathways and skin barrier mechanisms in AD pathogenesis, highlighting potential avenues for therapeutic innovation.

EPIGENETIC MODIFICATIONS AND ENVIRONMENTAL INFLUENCES

The role of epigenetics in the pathogenesis of AD is gaining increasing recognition, particularly in understanding how environmental factors such as allergens, infections, and pollutants[88] can modulate gene expression.[89,90] This modulation, driven by mechanisms such as DNA methylation and microRNA (miRNA) regulation, has been implicated in the differential expression of immune- and skin barrier–related genes, potentially explaining the varied clinical presentations and severity of AD among individuals.[91-94]

DNA methylation plays a critical role in immune regulation and skin barrier integrity within the pathogenesis of AD. Specifically, it controls keratinocyte proliferation and differentiation, both essential for maintaining the skin barrier. Key DNA methyltransferases, such as DNMT1, DNMT3A, and DNMT3B, establish and maintain DNA methylation patterns.[95] DNMT1 suppresses keratinocyte differentiation and maintains basal cell proliferation, while DNMT3A and DNMT3B bind to active enhancers in an H3K36me3-dependent manner to drive epidermal differentiation.[96,97] These mechanisms underscore the substantial role of DNA methylation in epidermal formation and homeostasis.[96,97]

DNA methylation patterns also modulate the expression of T_H2-related cytokines, central to AD's inflammatory response.[98] Epigenetic changes in regions that control T_H2 cytokine production, like the *RAD50* gene region, affect methylation at cytokine promoters, influencing IL-4, IL-5, and IL-13 expression.[99,100] This modulation can intensify T_H2-driven immune responses, exacerbating inflammation in AD patients. These shifts in cytokine expression contribute to persistent inflammation and the chronic nature of AD, especially in T_H2-dominant endotypes.

Hypermethylation of the *FLG* gene, encoding filaggrin, a key protein for skin barrier integrity, results in reduced filaggrin expression. Filaggrin deficiency strongly correlates with epidermal barrier dysfunction—a hallmark of AD—permitting increased allergen penetration, microbial colonization (notably by *Staphylococcus aureus*), and TEWL.[101] The interplay between genetic *FLG* mutations and epigenetic silencing through hypermethylation can further exacerbate barrier defects, increasing susceptibility to severe disease, including AD, which can develop as a complication of ichthyosis vulgaris.[101]

Maternal atopy influences offspring's risk of atopy through epigenetic and transcriptomic changes. Schedel et al[102] identified 165 differentially methylated regions and 139 differentially expressed genes in atopic mothers, with key roles in the interferon signaling pathway. Incorporating differentially methylated regions into risk models enhanced the prediction of AD in high-risk infants. Notably, 9 differentially expressed genes, including *MX1* and *IFI6,* were shared between atopic mothers and their high-risk children, emphasizing the role of maternal epigenetic transmission.

miRNAs are small noncoding RNAs that regulate gene expression by targeting mRNA for degradation or translation inhibition. Several miRNAs are key regulators of immune responses and skin barrier function in AD, making them promising therapeutic targets. miR-155 is significantly upregulated in AD lesions, promoting T_H2 immune responses by targeting immune-regulatory proteins and enhancing T_H2 cytokines like IL-4 and IL-13, which play major roles in AD pathophysiology.[103,104] Elevated miR-155 levels are linked to severe, treatment-resistant AD, suggesting modulation of miR-155 as a strategy to reduce inflammation in T_H2-dominant AD. Additionally, miR-155's role in T_H17 responses implicates it in T_H17-driven inflammatory endotypes, often associated with chronic or severe AD.[103] In contrast, miR-146a acts as a negative inflammation regulator by inhibiting the nuclear factor kappa B, aka NF-κB, pathway. It targets *IRAK1* and *TRAF6,* lowering proinflammatory cytokines and chemokines, correlating with reduced IgE levels and suggesting its value in managing mild or allergic-dominant AD endotypes.[105] Similarly, miR-124 also suppresses NF-κB, supporting its therapeutic potential for AD endotypes marked by chronic, nonacute inflammation.[106] miR-335, involved in regulating keratinocyte proliferation and differentiation, is downregulated in AD, contributing to epidermal barrier dysfunction.[107] This miRNA dysregulation and others, such as miR-29b (regulating keratinocyte apoptosis) and miR-10a-5p (balancing keratinocyte proliferation and differentiation), weaken skin barrier integrity, especially in intrinsic AD endotypes marked by barrier impairment.[108,109] Another important regulator of skin inflammation in AD is miR-939, which increases the expression of matrix metalloproteinases thereby promoting the colonization of *S aureus*.[110]

HUMAN MICROBIOME IN THE CLASSIFICATION OF ENDOTYPES IN AD

The skin and gut microbiomes play crucial roles in host immune regulation, impacting AD pathogenesis and progression. Studies comparing the microbiomes of healthy individuals and those with AD show significant differences in both skin and gut microbiota.[111-115] Similar alterations in mouse models further link microbiome changes to AD development.[116,117] Recent mechanistic studies reveal causal roles for specific bacteria in AD, supporting the potential of microbiome-based AD endotypes as promising tools for diagnosis and treatment.[11,118,119]

The skin microbiome is a complex ecosystem of bacteria, viruses, fungi, and archaea, crucial for maintaining community dynamics and resilience.[120,121] Early skin microbiomes are dominated by *streptococci* and *staphylococci*, with diversity increasing with age.[122,123] *Staphylococcus epidermidis* promotes homeostasis in early life, while disruptions in the skin microbiome are linked to AD.[124,125] *Staphylococcus aureus* overgrowth and reduced diversity are common in AD flares, with higher *S aureus* levels correlating with increased disease severity, peripheral blood IgE, CCL17, and eosinophil counts, indicating T_H2 deviation (Fig 2, *A*).[126-128] Recent studies reveal that *S aureus* proteases promote IL-17–producing eosinophils through IL-36α expression in keratinocytes, contributing to TEWL and reduced stratum corneum integrity. While *S aureus* mechanisms in AD are not fully understood, metabolic disorders involving purine and phenylalanine pathways may play a role.[118] *S aureus* can also induce itching by activating PAR1 receptors on pruriceptors, creating a feedback loop that worsens AD symptoms through increased skin damage and further *S aureus* infiltration.[129] Site-specific microbiome variations, such as *S aureus* abundance on posterior thigh compared to upper back, underscore the need to consider anatomical differences in AD studies.[130] *Staphylococcus epidermidis*, an important skin commensal, has been reported to play a role in preventing *S aureus* colonization and contributes to immune homeostasis

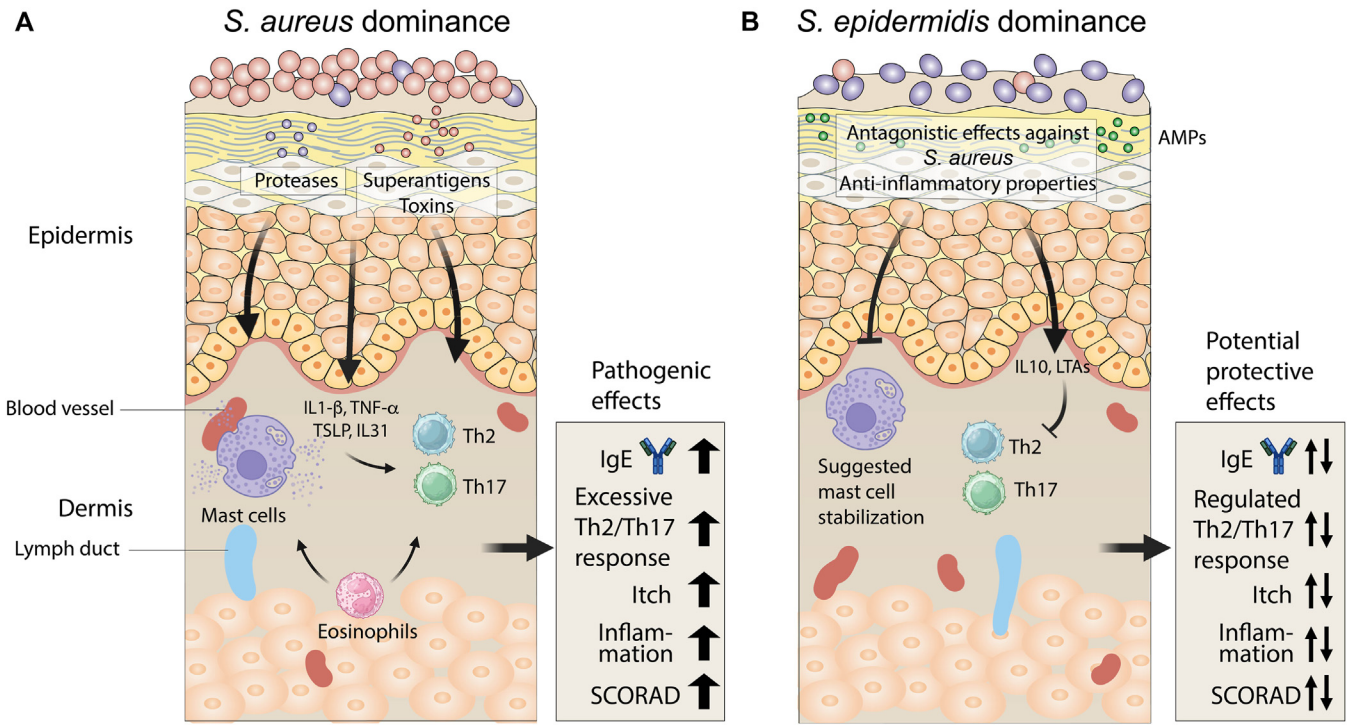

FIG 2. Schematic representation of immune dynamics and microbial dominance in skin inflammation, indicating divergent immune pathways associated with *Staphylococcus aureus* and *Staphylococcus epidermidis* dominance in skin. **(A)** Pathogenic effects of *S aureus* dominance, including elevated protease, superantigen, and toxin levels, which contribute to heightened inflammation, excessive T_H2/T_H17 response, and increased disease severity, reflected by SCORAD and itch scores. **(B)** Potential protective role of *S epidermidis* dominance, promoting balanced T_H2/T_H17 response, anti-inflammatory properties, and antagonism against *S aureus,* supporting immune homeostasis. Key immune mediators (eg, IL-1, TNF-α, TSLP, IL-31, IL-10) and cellular players (eg, mast cells, lymphocytes, eosinophils) are represented to underscore balance between inflammatory and regulatory pathways. *AMPs,* Antimicrobial peptides.

through the production of antimicrobial peptides (Fig 2, *B*).[131] Furthermore, *S epidermidis* has been shown to promote anti-inflammatory responses in the skin by enhancing the production of IL-10 while reducing the secretion of proinflammatory cytokines.[132] Such interactions within the AD microbiome help modulate immune responses in the skin, potentially mitigating excessive inflammation that may exacerbate AD symptoms.

Beyond the bacterial microbiome, the skin mycobiome has also been implicated in AD.[112,133] AD has been associated with dysbiosis in the skin mycobiota, with one study showing increased fungal community diversity in more severe AD.[134] The fungal species *Candida albicans* is more abundant in AD patients, and fungal species such as *Malassezia restricta, Malassezia globosa, Malassezia furfur,* and *Malassezia sympodialis* are frequently detected during AD flares.[135-139] A human observational study[140] found a reduction in *Malassezia* species to be associated with increased AD severity, revealing distinct clusters between patients with mild to moderate AD and those with severe AD, suggesting the existence of AD endotypes. Additionally, a positive correlation has been observed between higher serum IgE levels and proportions of *Ascomycota* in AD patients,[141] with high peripheral blood total IgE also being correlated with elevated *S aureus* levels. These findings suggest that endotyping AD according to fungal abundance and fungal interaction with skin bacteria is a promising avenue for future research.

The balance or dysbiosis of the gut microbiome influences protective versus proinflammatory responses in skin diseases via the gut–skin axis. Mouse studies show that modulating the gut microbiome with prebiotics and probiotics can reduce skin inflammation, suggesting that gut imbalances contribute to AD pathogenesis.[142,143] The gut microbiome affects the gut–skin axis through metabolite, immunologic, and neuroendocrine pathways.[144,145] Studies reveal lower levels of short-chain fatty acid–producing microbes like *bifidobacteria* and *Ruminococcus gnavus* in AD patients, with increased prevalence of *Staphylococcus aureus* and *Clostridium difficile.*[22,146-148] *Bifidobacteria*-produced GABA also inhibits skin itching.[149,150] Stratifying AD patients by gastrointestinal symptoms shows distinct gut bacterial profiles, with *Bacteroides, Bifidobacterium,* and *Faecalibacterium* more prominent in those with symptoms, suggesting gut microbiome–driven AD endotypes.[151] Consistent with skin microbiome findings, purine nucleotide degradation pathways are enriched in AD patients compared to healthy controls.[152]

CLINICAL AND EPIDEMIOLOGIC CHARACTERISTICS OF AD ENDOTYPES

AD is a highly heterogeneous condition, with diverse symptoms and trajectories. Symptoms include dry skin, hyperlinearity of the palms or soles, infraorbital folds, white dermographism,

facial pallor, and orbital darkening.[153] Although these physical markers are commonly associated with AD, they are not exclusive to the disorder; they may be absent in some AD patients and can appear in many other conditions, including atopic respiratory disease,[153] autoimmune disease,[154] and mental disorders.[155] The clinical presentation of AD varies significantly both between individuals and within the same individual, fluctuating throughout the course of the disease and across different age groups. While the existence of multiple AD phenotypes has long been recognized, their definitions remain unclear, and novel endotypes can be described (Fig 3).

AD subtypes in different age groups

More than 85% of all AD cases begin before the age of 5, with over 20% of children in industrialized countries affected.[15] In infants (under 2 years), AD typically presents within the first few months of life as seborrheic dermatitis on the cheeks and scalp; it may also affect the neck, trunk, and extensor areas. After age 2, lesions may remain acute but often become more lichenified, especially in flexural areas. Nummular plaques with oozing and crusts may appear on the hands and wrists. Compared to adult-onset AD, childhood-onset AD more frequently affects the face and may include conjunctivitis, eyelid dermatitis, pruritus after sweating, xeroderma, and hand and foot dermatitis, along with Dennie-Morgan lines.[156-159]

Most of our understanding of AD pathogenesis comes from adult studies, which is a shortcoming because the disease differs in children. In infants and toddlers with new-onset AD, infiltrating T cells and dendritic cells, including T_H2/T_H22-polarized populations, are present. Both children and adults with AD show an expansion of cutaneous lymphocyte-associated antigen (CLA)-positive T_H2 cells in peripheral blood.[160] However, adults experience an increase in both CLA^+ T_H1 and T_H2 cells, while children typically show low levels of CLA^+ T_H1 cells. Instead, infants and toddlers exhibit marked upregulation of T_H9 and T_H17 responses[161] and greater epidermal hyperproliferation compared to adults with chronic AD, as indicated by higher expression of keratin[16] and Ki-67.[162] As children age, the frequency of CLA^- T_H2 cells increases in the blood, indicating systemic immune activation and progression to chronic disease.[15] Skin barrier defects are common in infants with AD, but these are often unrelated to filaggrin deficiency, as filaggrin expression in young children is usually normal.[160]

In adults, AD typically manifests as chronic, lichenified, dry lesions on the head, neck, and flexural areas. The prevalence of AD among adults varies worldwide, with 10% affected in the United States in 2010[163] and rates ranging from 2% to 17% in other countries.[164-168]

Among individuals over 60, the prevalence is lower, between 1% and 3%, with men being more frequently affected.[169] Cutaneous transcriptomic studies suggest that adult AD can be categorized into 3 subgroups by age. As patients get older, T_H2/T_H22 activation in AD skin decreases, while T_H1/T_H17 activation increases. Additionally, epidermal abnormalities lessen with age, as markers of terminal differentiation increase and hyperproliferation markers decrease.[170] In older adults, lichenification often diminishes, with fewer lichenified lesions appearing in flexural areas.

Biomarkers associated with disease severity vary by age. In young adults (18-40 years), markers of T_H2, T_H1, and T_H17 activity strongly correlate with disease severity, but as patients get older, T_H17 signaling in the skin becomes more prominent.[170] These findings are supported by corresponding protein-level results in the blood.[171] Around 25% of adult AD cases are adult onset, likely representing a distinct endotype with immune mechanisms that remain to be fully identified.[15] Adult-onset AD is more likely to affect the extensor surfaces, head, and neck as well as the hands and feet.

Acute versus chronic AD

The clinical presentation of acute and chronic AD differs significantly. Molecular profiling of these subtypes reveals distinct differences. Acute AD is marked by a substantial increase in terminal differentiation proteins (S100As)[172] and T_H2/T_H22 cytokines.[54,158] In contrast, chronic AD shows even greater hyperproliferation (Ki-67),[172] intensified T_H2- and T_H1-related inflammation, and elevated IL-22 signaling.[54,158]

Disease trajectories, atopic march, and comorbidities

Various atopic disorders, including allergic asthma, rhinitis, and food allergies, may develop after the onset of AD. However, the underlying mechanisms that lead to these atopic comorbidities are not well understood.[173] They may involve defects in the skin barrier that predispose individuals to allergic sensitization, as well as abnormal T_H2 immune signaling. The earlier onset of AD compared to asthma or allergic rhinitis suggests a causal relationship, indicating that AD may serve as a gateway to other, later-developing atopic conditions.

Recent research utilizing machine learning has identified distinct patient clusters or endotypes. The PASTURE study found that the presence of food allergies and a persistent AD phenotype are risk factors for the progression of airway type 2.[174] A meta-analysis of multiple cohorts further supported these findings. By combining data from over 10,000 children in the United Kingdom and the Netherlands, one study showed that children with persistent AD had elevated IgE levels and the highest likelihood of developing coexisting asthma.[175] Additionally, another study that used Bayesian machine learning confirmed that persistence of AD and sensitization are significant risk factors for the atopic march.[176]

Pruritus and AD

Pruritus (itch) is a distressing and impactful symptom of AD, significantly affecting quality of life across various AD endotypes and phenotypes.[177] The underlying mechanisms of itch vary with disease chronicity, immune profile, and specific endotype.[13,178]

At the molecular level, IL-31 is a central driver of pruritus in AD.[179-182] It acts on sensory neurons through its receptor on keratinocytes and neurons, amplifying itch through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway. This effect is pronounced in T_H2-driven endotypes, where IL-31 expression is elevated, contributing to more severe pruritus. JAK inhibitors, which block the JAK/STAT pathway involved in IL-31 signaling, have shown effectiveness in managing itch in cytokine-driven, T_H2-dominant AD cases.[183] Therapies like dupilumab and JAK inhibitors have successfully reduced pruritus by targeting these itch pathways.

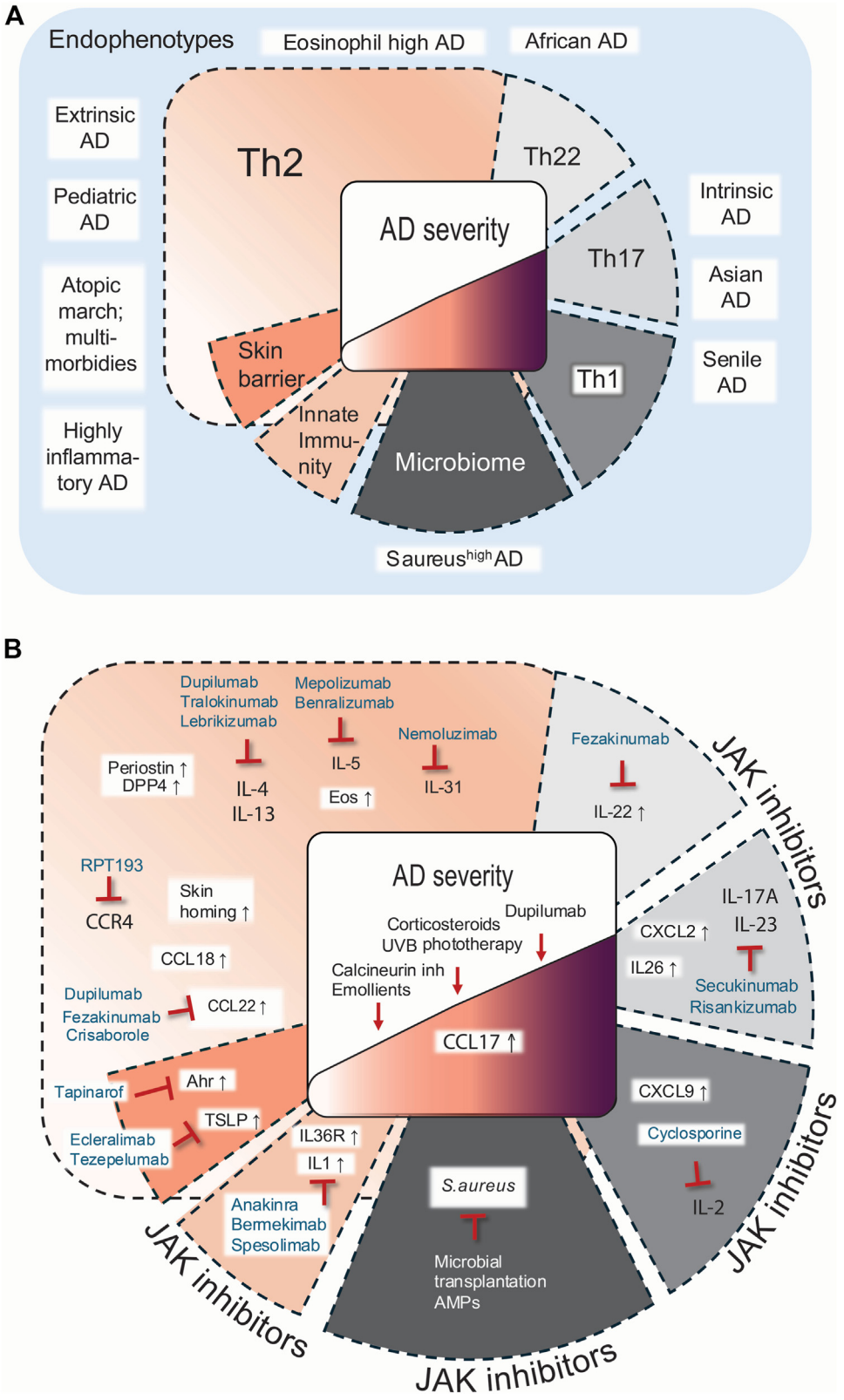

FIG 3. Pathogenetic pathways, immune endotypes, and targeted treatments in AD. **(A)** AD endotypes classified by immune response and microbiome interactions. AD is predominantly T_H2 driven, but T_H1, T_H17, and T_H22 pathways contribute in nonclassical and mixed endotypes. Microbiome dysbiosis, particularly *Staphylococcus aureus* overgrowth, influences disease severity and immune activation. Endophenotypes such as eosinophil-high AD, intrinsic AD, and pediatric AD highlight variability in clinical presentation and treatment response. **(B)** Targeted therapies based on immune endotypes. T_H2-dominant AD is treated

Another key mechanism involves the PAR-2 (protease-activated receptor 2) pathway, triggered by proteases from damaged keratinocytes in cases of barrier dysfunction, such as those with filaggrin deficiency. Protease release activates PAR-2, worsening itch and contributing to chronic pruritus.[184] Additionally, *Staphylococcus aureus* can independently initiate itch via PAR1 receptors, setting off a scratch-induced feedback loop that exacerbates AD symptoms and makes the skin more susceptible to *S aureus* infiltration.[185,186] Despite the more severe phenotype often observed in *S aureus*–positive cases, studies like that of Simpson et al[127] indicate that itch severity can occur independently of *S aureus* colonization, emphasizing that pruritus in AD is multifactorial and not solely driven by microbial presence.

DIAGNOSTIC TOOLS, BIOMARKERS, AND THERAPEUTIC APPROACHES IN AD

Although AD is a clinically diverse condition, most treatments still follow a one-size-fits-all approach. Standard therapy typically includes the use of emollients, allergen avoidance, and patient education. For mild AD, treatment options include topical corticosteroids, the calcineurin inhibitors tacrolimus and pimecrolimus, and more recently the PDE4 inhibitor crisaborole.[187] In more severe cases, treatment may involve ultraviolet phototherapy or systemic immunosuppressants such as cyclosporine A, methotrexate, azathioprine, and mycophenolate mofetil. The recent approval of biologics like dupilumab and tralokinumab, along with JAK inhibitors such as upadacitinib, abrocitinib, and baricitinib, has expanded treatment options for moderate to severe AD.[188,189] While dupilumab and tralokinumab target specific immune pathways, JAK inhibitors act more broadly, using small molecules to modulate multiple pathways (Fig 3, and see Table E1 in this article's Online Repository at www.jacionline.org).

Despite these options, there is no current strategy to target specific AD phenotypes or endotypes, a gap that precision medicine aims to address. Developing reliable biomarkers for personalized treatment is essential for improving prevention strategies, selecting effective therapies, and determining the timing of medication adjustments.[30] AD's complexity leads to variable treatment responses (Fig 3), with some patients experiencing adverse effects from unnecessarily high doses in those with poor disease response to therapy. Precision medicine aims to provide the right drug at the correct dosage to the appropriate patient at the optimal time.

A new disease-modification concept is emerging that seeks to alter the course of AD by targeting the underlying processes that drive the disease.[190] This approach highlights the importance of using validated biomarkers to track disease progression and guide treatment decisions. Meanwhile, drug development should focus on understanding the pathophysiologic mechanisms behind AD endotypes, enabling more precise and effective therapies.

Diagnostic tools and severity scoring

The management of AD largely depends on physician assessments and severity scores like the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD),[191,192] which are widely used but often fail to capture detailed endophenotypes. Clinician interpretations can be subjective, and although prescribing biologics and small-molecule drugs is based on disease severity, this does not always align with the underlying endotype. Better classifications of AD subgroups could improve predictions of treatment response and reduce adverse effects for patients with disease unlikely to benefit from certain therapies. Consequently, new biomarkers are needed to refine AD endotype classification and improve precision in treatment selection.

Biomarker discovery and use

The search for AD biomarkers is still in its early stages.[193] While biomarkers like thymus and activation-regulated chemokine (TARC) are already being used in clinical practice, most candidates are still under development. Screening for these biomarkers can help identify individuals at risk and guide treatment. For example, TEWL has shown promise as a noninvasive biomarker,[194] and around 30% of AD patients carry filaggrin mutations, with polymorphisms in *TLR2* also being associated with AD.[74] However, there is still no biomarker available to confirm an AD diagnosis. Differential biomarkers, such as carbonic anhydrase II, or CAII, which is highly expressed in AD compared to psoriasis, have been developed,[195] and urinary lipid profiles may also aid in diagnosis.

Established and emerging biomarkers for severity

Numerous biomarkers have been identified for assessing AD severity.[27,28,30,193,196-198] These include TARC/CCL17,[199,200] MDC/CCL22 (macrophage-derived chemokine),[201] CTACK/CCL27 (cutaneous T-cell–attracting chemokine),[201,202] eotaxin/CCL26 (eosinophil chemotactic protein),[203] IL-13,[204] IL-31,[58,205] IL-33,[202] IL-22,[45,170] IL-18,[206] IL-19,[160,207] IL-16,[208] periostin,[36,204,209] S100A proteins,[210,211] matrix metalloproteinases,[207,210] and lactate dehydrogenase.[30,200] TARC and MDC are among the best established and are both associated with T_H2-mediated inflammation and correlated with disease severity.[200,212] Elevated IL-13 levels, a key T_H2 cytokine driving inflammation and skin barrier dysfunction, are predictive of treatment responses to IL-4/IL-13–targeting therapies such as dupilumab.[36] Similarly, IL-22, involved in epidermal hyperplasia and barrier defects, is emerging as a key biomarker of AD severity.[45,46]

Emerging biomarkers, such as periostin,[178,204,209,213] are gaining attention for their role in chronic inflammation, itch, and tissue remodeling. Ras-associated binding protein 25, or RAB25, a

with dupilumab, tralokinumab, and nemolizumab (targeting IL-4, IL-13, and IL-31). IL-5 inhibitors (mepolizumab, benralizumab) may benefit eosinophilic AD. RPT193 targets CCR4 in T-cell–rich pediatric AD. T_H22-driven AD involves epidermal hyperplasia and IL-22 upregulation, with potential treatments such as fezakinumab targeting IL-22. T_H17-associated AD may be defined by CXCL2 and IL-26 upregulation, with secukinumab and risankizumab as potential therapies. T_H1-skewed AD is associated with CXCL9 expression and may be treated with cyclosporine. Microbiome-based interventions (antimicrobial peptides, phage therapy) counteract *S aureus* overgrowth. Treatments for skin barrier and innate immunity defects include tezepelumab (TSLP), bermekimab (IL-1), and spesolimab (IL-36). Mild cases benefit from emollients and topical therapies, while severe cases require systemic treatments such as biologics, JAK inhibitors, or immunosuppressants. *CXCL,* C-X-C motif chemokine ligand.

novel marker linked to epidermal barrier dysfunction, has shown significant potential, with low expression correlating with higher EASI scores, making it useful for assessing disease severity.[214] Further, *Malassezia*-specific IgE has been associated with the development of dupilumab-associated head and neck dermatitis and thus can be used to predict this disorder before dupilumab treatment.[215]

Therapeutic approaches

Over the past two decades, significant progress has been made in understanding the complex mechanisms underlying AD, leading to new potential targets for pharmacologic and therapeutic interventions. AD encompasses a wide range of disease phenotypes and endotypes, involving multiple interacting factors, including environmental exposures, skin microbiome, epidermal barrier, and immune response, all of which present opportunities for prevention and treatment.

Targeting skin microbiome for therapeutic intervention

Several strategies have been proposed to modulate the skin microbiome. One approach involves bacteria replacement therapy, such as applying gram-negative *Roseomonas mucosa* to AD-affected skin, which promotes tissue repair and immune regulation through Toll-like receptor 5 signaling.[216] Another strategy uses specific *Staphylococcus* strains that target *S aureus,* eliminating bacteria and inhibiting its toxin production.[217] Additionally, synthetic antimicrobial peptides are being developed as potential topical agents to combat dysbiosis.[218] Beyond topical treatments, oral therapies are also being explored. One example currently in phase 1 clinical trials is a nonlive preparation of *Prevotella histicola* (EDP1815), designed to induce immune regulation in the small intestine.[219]

Restoring epidermal barrier integrity

A defining feature of AD is dry, highly permeable skin, which results from a disrupted epidermal barrier caused by genetic factors or chronic inflammation. Strategies to restore barrier function focus on two main approaches: replenishing essential epidermal components and targeting underlying inflammatory pathways. One promising strategy is controlling IL-13 signaling, which contributes to barrier dysfunction through a periostin- and JAK/STAT-dependent mechanism.[220] However, while addressing underlying inflammation helps, it does not fully restore the epidermal barrier. Unfortunately, the biochemical changes and structural defects driving epidermal barrier impairment are not well understood, presenting a significant challenge in developing effective therapies. As of now, emollients remain the primary method to improve barrier function.

One potential research avenue is involves hyaluronan, a natural polymer with diverse biological functions, which is currently being investigated for its role in inflammatory diseases.[221] An interesting target in this context is *TNFAIP6,* a gene induced by T_H2 cytokines that encodes the protein TSG-6 (TNF-α–stimulated gene 6), which sequesters hyaluronan between epidermal cells in response to inflammation.[222] Modulating *TNFAIP6* activity could provide a novel approach to restoring the epidermal barrier in certain AD subtypes.

Modulating innate immune response

Keratinocyte-derived alarmins, such as TSLP, IL-33, and IL-25, are promising therapeutic targets because of their role in triggering inflammation. While TSLP-targeting antibodies like tezepelumab have shown strong efficacy in asthma treatment,[223] their effectiveness in AD has been less convincing.[224] IL-33 is another potential target because it plays a key role in early innate immune responses. In a study involving 12 patients with moderate to severe AD, a single dose of the anti–IL-33 antibody etokimab led to significant improvement, with effects lasting up to 140 days.[225]

IL-1α, released by keratinocytes after skin injury, has been explored as a therapeutic target for AD. Treatment with the anti–IL-1α antibody bermekimab in preclinical and early clinical trials showed promising results, with a significant number of patients experiencing clear or nearly clear skin and substantial itch reduction.[226]

Another key player in innate immunity, IL-36, is upregulated in AD and has been linked to *Staphylococcus aureus* colonization in a mouse model.[227] Spesolimab, an IL-36 pathway inhibitor, was evaluated in a study involving 51 AD patients, demonstrating improvements in EASI scores from baseline.[228]

Finally, the aryl-hydrocarbon receptor (AhR) plays a dual role in the pathophysiology of various skin disorders, with both pro- and anti-inflammatory effects depending on the ligand and context. Coal tar has been shown to activate AhR, leading to the restoration of filaggrin expression. Similarly, tapinarof, a natural AhR agonist, helps reduce inflammation and has been shown to improve AD symptoms in humans.[229]

Harnessing the adaptive immune response

The adaptive immune system, from antigen presentation to downstream signaling pathways, presents multiple therapeutic targets for AD. The advent of biologics like dupilumab[33-35,38,230-233] has significantly improved outcomes for some AD patients, yet the disease of a substantial portion remains unresponsive.[230,234] Large clinical trials show that dupilumab results in EASI-75 and EASI-90 responses in only 44-65% and 30-51% of patients, respectively.[235] This outcome gap highlights the need for treatments tailored to specific AD endotypes, particularly non–T_H2-driven AD. Precision medicine offers promising solutions by targeting specific immune pathways.

New treatments have emerged, including tralokinumab,[24,39,40,41,204,236] approved by the European Medicines Agency in 2021, which targets IL-13 and has shown efficacy in patients with long disease histories and previous multidrug failures.[42] Lebrikizumab is another high-affinity IgG_4 monoclonal antibody targeting IL-13.[237] By inhibiting the IL-4Rα and IL-13Rα1 receptor signaling complex, it reduces type 2 cytokine–driven inflammation.[238] In two phase 3 trials (ADvocate1 and ADvocate2), lebrikizumab significantly improved outcomes in adolescents and adults with moderate to severe AD. With a favorable safety profile compared to JAK inhibitors, lebrikizumab is a promising addition to biologic therapies, complementing treatments such as dupilumab and tralokinumab.[39]

Eosinophils are thought to play a key role as effector cells in AD. As a result, targeting IL-5, with a central role in promoting eosinophil differentiation, recruitment, survival, and degranulation, has been explored as a potential therapeutic approach. However, in a clinical trial, the anti–IL-5 antibody mepolizumab

did not lead to a reduction in clinical severity despite significantly lowering peripheral blood eosinophil levels.[239]

While T_H2 immune polarization is central to AD, other mediators such as IL-17, IL-23, and IL-22—more commonly associated with psoriasis—are also being investigated for potential treatment strategies. IL-22, which is induced by *S aureus* exotoxins, correlates with AD severity.[240] In keratinocytes, IL-22 suppresses filaggrin expression, contributing to barrier dysfunction.[241] A clinical trial using the anti–IL-22 antibody fezakinumab showed promising results in patients with severe AD.[242] Fezakinumab[45] treatment significantly reduced SCORAD in phase 2a clinical trials for severe AD but had lesser effects in moderate AD cases.[243]

Although the IL-23/IL-17 axis is a key pathway in psoriasis, it may also play a role in certain AD subtypes, such as intrinsic AD and cases more common in Asian populations. However, a trial evaluating secukinumab in moderate to severe AD failed to demonstrate clinical efficacy.[244] Interestingly, in patients with plaque psoriasis, secukinumab treatment has been linked to eczematous-like reactions,[245] highlighting the need for careful monitoring of this potential adverse effect. Similarly, another study investigating the IL-23 inhibitor risankizumab in AD also showed no clinical benefit.[246]

Modulating T-cell migration

Antigen-specific T cells make up a significant portion of the immune cells infiltrating AD lesions, where they contribute to local inflammation and disrupt epidermal barrier function. Their recruitment is driven by chemotactic signals, making the inhibition of T-cell migration a promising therapeutic strategy.

The C-C chemokine receptor 4 (CCR4), a key marker of memory T_H2 cells, binds to chemokines such as CCL5/RANTES, CCL2/MCP1, CCL22/MDC, and CCL17/TARC, which are highly elevated in AD. Blocking CCR4 is therefore an attractive treatment approach. In a clinical study, oral administration of RPT193, a selective T_H2 recruitment inhibitor, led to significant clinical improvements in AD patients, along with beneficial modulation of the skin transcriptomic profile.[247]

Targeting itch relief

IL-31, a pruritogenic cytokine produced by infiltrating T_H2 cells, plays a central role in AD-related itching, with its levels correlating to disease severity. Blocking IL-31 has emerged as a strategy to control pruritus. In a clinical trial, treatment with the anti–IL-31 receptor alpha antibody nemolizumab effectively reduced itching but did not significantly decrease inflammation, as measured by clinical scores.[248]

Targeting multiple signaling pathways

The Janus kinase family, comprising JAK1, JAK2, JAK3, and TYK2 (tyrosine kinase 2), plays a central role in various signaling pathways. JAK inhibitors are effective because they block receptors across multiple pathways, and over 90 JAK inhibitors are currently patented, many in clinical development for inflammatory diseases. JAK inhibitors for AD treatment are classified into 3 categories: nonselective (pan) JAK inhibitors, dual inhibitors (JAK1/JAK2), and selective JAK1 inhibitors (Table E1), which can be applied topically or orally.

Ruxolitinib, a dual JAK1/JAK2 inhibitor applied as a cream for mild to moderate AD, has shown clinical efficacy, including sustained itch reduction and safety in both adults and children.[249] Another example, baricitinib, is an oral JAK1/JAK2 inhibitor.[33,39,189] In phase 3 trials for adults with moderate to severe AD inadequately controlled by corticosteroids, baricitinib demonstrated significant improvements in disease severity.[250]

JAK inhibitors have the potential to transform AD care, with current phase 3 data suggesting JAK1-selective inhibitors may offer greater efficacy than dual JAK1/JAK2 inhibitors. This could be because of dual JAK inhibitors block JAK2-associated IL-10 receptors, inhibiting IL-10 signaling, which plays a crucial role in inflammation control and tolerance induction.

Addressing comorbidities

Associated comorbidities,[251,252] such as asthma, rhinitis, and food allergies, complicate AD management. This progression, known as the atopic march,[173] is not experienced by all patients, and biomarkers to identify individuals at risk for this progression are still lacking.[30,253] A deeper understanding of the mechanisms that drive the transition from skin sensitization to respiratory allergic diseases is needed to develop disease-specific therapies and preventive strategies.

CHALLENGES IN ENDOTYPE CLASSIFICATION OF AD

Endotype classification in AD presents numerous challenges, especially when considering its clinical utility. AD is a highly heterogeneous condition characterized by a range of clinical phenotypes, which vary according to age, ethnicity, disease severity, and immune response patterns.[10] The classification of AD into endotypes, defined by distinct molecular mechanisms and immunologic pathways, offers the potential to personalize treatment strategies (Fig 3). However, significant limitations hinder its widespread clinical application.

One of the primary challenges in endotyping AD is the complexity of its underlying immunopathology. AD involves a dynamic interplay between immune dysregulation, barrier dysfunction, genetic predispositions, and environmental factors. Various immune pathways, such as T_H2, T_H22, T_H17, and T_H1 responses, have been implicated in different subsets of AD. However, these immune signatures are not always exclusive, and mixed immune responses may be evident. As a result, identifying clear-cut endotypes becomes challenging, limiting the predictive value of these classifications for guiding clinical decisions.

Another limitation lies in the variability of biomarkers used to define endotypes. Although several biomarkers, such as cytokines (eg, IL-4, IL-13, IL-17), chemokines, and transcriptomic signatures, have been proposed for endotyping AD, there is no consensus on which biomarkers are the most reliable or clinically relevant. Furthermore, the biomarkers associated with AD endotypes often fluctuate over time and with disease severity, further complicating their use for stable classification. This dynamic nature of AD exacerbates the difficulty in developing robust, reproducible endotype classifications that can be applied consistently across patient populations.

Additionally, the limited accessibility and cost of advanced diagnostic tools are barriers to the widespread use of AD endotyping in clinical practice. Endotype classification often

relies on molecular and genetic analyses, such as transcriptomic or proteomic profiling, which are not readily available in many clinical settings. These methods also require significant expertise and infrastructure, making them impractical for routine use in general dermatology clinics. This creates a gap between the theoretical potential of AD endotypes and their real-world application in patient care.

Moreover, there is a lack of longitudinal studies that track the stability of AD endotypes over time. The temporal dynamics of AD raise the question of whether endotypes identified at one point in time remain consistent throughout the disease course. This variability further complicates efforts to tailor long-term treatments according to initial endotype classification.

In conclusion, while the concept of AD endotyping holds promise for enhancing personalized medicine, significant challenges remain. The complexity of immune responses, variability in biomarkers, limited access to advanced diagnostics, and dynamic nature of the disease all hinder the clinical utility of AD endotype classification.

CONCLUSION AND FUTURE DIRECTIONS

AD, like asthma, represents a spectrum of diseases defined by diverse mechanistic pathways (endotypes) and variable clinical presentations (phenotypes). Defining these endotypes is essential to advancing personalized treatments tailored to each patient's unique immune, genetic, and molecular characteristics.

Genetic factors,[86,93,254,255] such as *FLG* mutations,[64,231] significantly affect AD endotypes, especially in European/American populations. However, overlapping genetic profiles between AD subtypes indicate that genetics alone cannot fully delineate AD endotypes. Polymorphisms in genes like *TLR2, SPINK5,* and *TSLP* add to the complexity. Although genotyping remains costly, advances in technology are improving the accessibility of genetic profiling, bringing precision medicine in AD care closer to reality.

Transcriptomic studies[23,24,256] highlight critical aspects of AD, including epidermal dysfunction, itch signaling, and T_H2 immunity, and identify distinct endotypes driven by T_H2, T_H1, and T_H17/T_H22 immune responses. However, reproducibility of endotype definitions remains challenging. Concurrent serum and blood transcriptomic analyses reveal distinct inflammatory profiles, underscoring AD's complexity and heterogeneity.

In summary, refining endotype-specific diagnostic tools and treatments presents a transformative opportunity for AD management. Research expansion through multiomics integration, long-term patient cohorts, and studies on underrepresented populations will provide deeper insight into AD endotypes. These advancements promise a more precise, individualized approach to AD treatment, improving outcomes for this complex disease.

Emerging research areas hold significant potential for improving AD diagnosis, treatment, and understanding, as follows:

- Multiomics integration—Combining genomics, proteomics, metabolomics, and epigenomics could yield new biomarkers and molecular profiles for AD endotypes, advancing personalized treatment.
- Longitudinal studies—Tracking immune, genetic, and environmental factors over time can clarify how AD endotypes evolve, enabling early interventions and targeted therapies.
- Ethnic and geographic diversity—Expanding studies to underrepresented populations will uncover unique factors influencing AD, fostering more inclusive and effective treatments.
- Microbiome interactions—Understanding how skin and gut microbiomes affect immune responses may lead to novel microbiome-targeted therapies for specific AD endotypes.
- Endotype-specific therapies—Beyond dupilumab for T_H2-dominant AD, new treatments targeting critical pathways are needed for more resistant endotypes.

As our understanding of AD endotypes deepens, integrating precision medicine into routine care is increasingly feasible. Reliable biomarkers for AD diagnosis, severity prediction, and treatment response assessment will be central to this transformation. Advances in machine learning and artificial intelligence will enable predictive models that are based on patient-specific data, making personalized care a reality for AD patients.

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REFERENCES

1. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. Ann Allergy Asthma Immunol 2021;126:417-28.e2.
2. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study, 1990-2017. Br J Dermatol 2021;184:304-9.
3. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab 2015;66(suppl 1):8-16.
4. Tian J, Zhang D, Yang Y, Huang Y, Wang L, Yao X, et al. Global epidemiology of atopic dermatitis: a comprehensive systematic analysis and modelling study. Br J Dermatol 2023;190:55-61.
5. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The burden of atopic dermatitis: summary of a report for the National Eczema Association. J Invest Dermatol 2017;137:26-30.
6. Kern C, Wan J, LeWinn KZ, Ramirez FD, Lee Y, McCulloch CE, et al. Association of atopic dermatitis and mental health outcomes across childhood: a longitudinal cohort study. JAMA Dermatol 2021;157:1200-8.
7. Schonmann Y, Mansfield KE, Hayes JF, Abuabara K, Roberts A, Smeeth L, et al. Atopic eczema in adulthood and risk of depression and anxiety: a population-based cohort study. J Allergy Clin Immunol Pract 2020;8:248-57.e16.
8. Afshari M, Kolackova M, Rosecka M, Celakovska J, Krejsek J. Unraveling the skin; a comprehensive review of atopic dermatitis, current understanding, and approaches. Front Immunol 2024;15:1361005.
9. Feldman SR, Strowd LC, Lovell KK, editors. Management of atopic dermatitis: methods and challenges. Cham (Switzerland): Springer; 2024.
10. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020;396:345-60.
11. Geoghegan JA, Irvine AD, Foster TJ. *Staphylococcus aureus* and atopic dermatitis: a complex and evolving relationship. Trends Microbiol 2018;26:484-97.
12. Alvarenga JM, Bieber T, Torres T. Emerging biologic therapies for the treatment of atopic dermatitis. Drugs 2024; 84:1379-94..
13. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers 2018;4:1.
14. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol 2019; 143:1-11.
15. Nomura T, Wu J, Kabashima K, Guttman-Yassky E. Endophenotypic variations of atopic dermatitis by age, race, and ethnicity. J Allergy Clin Immunol Pract 2020;8:1840-52.
16. Choi SJ, Song MG, Sung WT, Lee DY, Lee JH, Lee ES, et al. Comparison of transepidermal water loss, capacitance and pH values in the skin between intrinsic and extrinsic atopic dermatitis patients. J Korean Med Sci 2003;18:93-6.
17. Marenholz I, Kerscher T, Bauerfeind A, Esparza-Gordillo J, Nickel R, Keil T, et al. An interaction between filaggrin mutations and early food sensitization improves the prediction of childhood asthma. J Allergy Clin Immunol 2009;123: 911-6.

18. Park JH, Choi YL, Namkung JH, Kim WS, Lee JH, Park HJ, et al. Characteristics of extrinsic vs intrinsic atopic dermatitis in infancy: correlations with laboratory variables. Br J Dermatol 2006;155:778-83.
19. Kabashima-Kubo R, Nakamura M, Sakabe J, Sugita K, Hino R, Mori T, et al. A group of atopic dermatitis without IgE elevation or barrier impairment shows a high Th1 frequency: possible immunological state of the intrinsic type. J Dermatol Sci 2012;67:37-43.
20. Reinhold U, Kukel S, Goeden B, Neumann U, Kreysel HW. Functional characterization of skin-infiltrating lymphocytes in atopic dermatitis. Clin Exp Immunol 1991;86:444-8.
21. Kim J, Ahn K. Atopic dermatitis endotypes: knowledge for personalized medicine. Curr Opin Allergy Clin Immunol 2022;22:153-9.
22. Lee E, Kim JH, Lee SY, Lee SH, Park YM, Oh HY, et al. Developmental trajectories of atopic dermatitis with multiomics approaches in the infant gut: COCOA birth cohort. J Allergy Clin Immunol 2025; 155:557-68..
23. Hawkins K, David E, Glickman JW, Del Duca E, Guttman-Yassky E, Krueger JG. Atopic dermatitis stratification: current and future perspective on skin and blood transcriptomic and proteomic profiling. Expert Rev Clin Immunol 2024;20:1083-8.
24. Cabrera-Perez JS, Carey VJ, Odejide OO, Singh S, Kupper TS, Pillai SS, et al. Integrative epidemiology and immunotranscriptomics uncover a risk and potential mechanism for cutaneous lymphoma unmasking or progression with dupilumab therapy. J Allergy Clin Immunol 2024.
25. Kim JE, Lee J, Huh YJ, Kim K, Chaparala V, Krueger JG, et al. Genomic profiling of the overlap phenotype between psoriasis and atopic dermatitis. J Invest Dermatol 2024;144:43-52.e6.
26. Facheris P, Da Rosa JC, Pagan AD, Angelov M, Del Duca E, Rabinowitz G, et al. Age of onset defines two distinct profiles of atopic dermatitis in adults. Allergy 2023;78:2202-14.
27. Song B, Ning X, Guo L, Liu W, Jin H. Comparative proteomics analysis reveals distinct molecular phenotype and biomarkers in patients with erythrodermic atopic dermatitis and erythrodermic psoriasis. Inflammation 2025;48:331-45.
28. Berdyshev E, Kim J, Kim BE, Goleva E, Lyubchenko T, Bronova I, et al. Stratum corneum lipid and cytokine biomarkers at age 2 months predict the future onset of atopic dermatitis. J Allergy Clin Immunol 2023;151:1307-16.
29. Aizat WM, Ismail I, Noor NM. Recent development in omics studies. Adv Exp Med Biol 2018;1102:1-9.
30. Park CO, Kim SM, Lee KH, Bieber T. Biomarkers for phenotype–endotype relationship in atopic dermatitis: a critical review. EBioMedicine 2024;103:105121.
31. Hui-Beckman JW, Goleva E, Berdyshev E, Leung DYM. Endotypes of atopic dermatitis and food allergy. J Allergy Clin Immunol 2023;151:26-8.
32. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, DeBenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol 2009;124:R7-12.
33. Tsai SY, Phipatanakul W, Hawryluk EB, Oyoshi MK, Schneider LC, Ma KS. Comparative safety of oral Janus kinase inhibitors versus dupilumab in patients with atopic dermatitis: a population-based cohort study. J Allergy Clin Immunol 2024;154:1195-203.e3.
34. Starrenburg ME, Bel Imam M, Lopez JF, Buergi L, Nguyen NT, Nouwen AEM, et al. Dupilumab treatment decreases MBC2s, correlating with reduced IgE levels in pediatric atopic dermatitis. J Allergy Clin Immunol 2024;154:1333-8.e4.
35. Geba GP, Li D, Xu M, Mohammadi K, Attre R, Ardeleanu M, et al. Attenuating the atopic march: meta-analysis of the dupilumab atopic dermatitis database for incident allergic events. J Allergy Clin Immunol 2023;151:756-66.
36. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143:155-72.
37. Wu Y, Gu C, Wang S, Yin H, Qiu Z, Luo Y, et al. Serum biomarker-based endotypes of atopic dermatitis in China and prediction for efficacy of dupilumab. Br J Dermatol 2023;188:649-60.
38. Traidl S, Harries L, Kienlin P, Begemann G, Roesner LM, Werfel T. Dupilumab strengthens herpes simplex virus type 1–specific immune responses in atopic dermatitis. J Allergy Clin Immunol 2023;152:1460-9.e5.
39. Chu AWL, Wong MM, Rayner DG, Guyatt GH, Díaz Martinez JP, Ceccacci R, et al. Systemic treatments for atopic dermatitis (eczema): systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol 2023;152:1470-92.
40. David E, Ungar B, Renert-Yuval Y, Facheris P, Del Duca E, Guttman-Yassky E. The evolving landscape of biologic therapies for atopic dermatitis: present and future perspective. Clin Exp Allergy 2023;53:156-72.
41. Pezzolo E, Gambardella A, Guanti M, Bianchelli T, Bertoldi A, Giacchetti A, et al. Tralokinumab shows clinical improvement in patients with prurigo nodularis-like phenotype atopic dermatitis: a multicenter, prospective, open-label case series study. J Am Acad Dermatol 2023;89:430-2.
42. Pereyra-Rodriguez JJ, Herranz P, Ruiz-Villaverde R, Elosua-Gonzalez M, Galan-Gutierrez M, Figueras-Nart I, et al. Treatment of severe atopic dermatitis with tralokinumab in clinical practice: short-term effectiveness and safety results. Clin Exp Dermatol 2023;48:991-7.
43. Brunner PM, Leung DYM, Guttman-Yassky E. Immunologic, microbial, and epithelial interactions in atopic dermatitis. Ann Allergy Asthma Immunol 2018;120:34-41.
44. Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part I: clinical and pathologic concepts. J Allergy Clin Immunol 2011;127:1110-8.
45. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J Allergy Clin Immunol 2019;143:142-54.
46. Laska J, Tota M, Lacwik J, Sedek L, Gomulka K. IL-22 in Atopic dermatitis. Cells 2024;13.
47. Nograles KE, Zaba LC, Shemer A, Fuentes-Duculan J, Cardinale I, Kikuchi T, et al. IL-22–producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing T_H17 T cells. J Allergy Clin Immunol 2009;123:1244-52.e2.
48. Malhotra N, Yoon J, Leyva-Castillo JM, Galand C, Archer N, Miller LS, et al. IL-22 derived from gammadelta T cells restricts *Staphylococcus aureus* infection of mechanically injured skin. J Allergy Clin Immunol 2016;138:1098-107.e3.
49. Esaki H, Brunner PM, Renert-Yuval Y, Czarnowicki T, Huynh T, Tran G, et al. Early-onset pediatric atopic dermatitis is T_H2 but also T_H17 polarized in skin. J Allergy Clin Immunol 2016;138:1639-51.
50. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased T_H17 polarization. J Allergy Clin Immunol 2015;136:1254-64.
51. Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? Curr Opin Immunol 2017;48:68-73.
52. Chan TC, Sanyal RD, Pavel AB, Glickman J, Zheng X, Xu H, et al. Atopic dermatitis in Chinese patients shows T_H2/T_H17 skewing with psoriasiform features. J Allergy Clin Immunol 2018;142:1013-7.
53. Huang J, Choo YJ, Smith HE, Apfelbacher C. Quality of life in atopic dermatitis in Asian countries: a systematic review. Arch Dermatol Res 2022;314:445-62.
54. Sanyal RD, Pavel AB, Glickman J, Chan TC, Zheng X, Zhang N, et al. Atopic dermatitis in African American patients is T_H2/T_H22-skewed with T_H1/T_H17 attenuation. Ann Allergy Asthma Immunol 2019;122:99-110.e6.
55. Thijs JL, Strickland I, Bruijnzeel-Koomen C, Nierkens S, Giovannone B, Csomor E, et al. Moving toward endotypes in atopic dermatitis: identification of patient clusters based on serum biomarker analysis. J Allergy Clin Immunol 2017;140:730-7.
56. Bakker DS, Nierkens S, Knol EF, Giovannone B, Delemarre EM, van der Schaft J, et al. Confirmation of multiple endotypes in atopic dermatitis based on serum biomarkers. J Allergy Clin Immunol 2021;147:189-98.
57. Bakker DS, de Graaf M, Nierkens S, Delemarre EM, Knol E, van Wijk F, et al. Unraveling heterogeneity in pediatric atopic dermatitis: identification of serum biomarker based patient clusters. J Allergy Clin Immunol 2022;149:125-34.
58. Möbus L, Rodriguez E, Harder I, Boraczynski N, Szymczak S, Hübenthal M, et al. Blood transcriptome profiling identifies 2 candidate endotypes of atopic dermatitis. J Allergy Clin Immunol 2022;150:385-95.
59. Lefèvre-Utile A, Saichi M, Oláh P, Delord M, Homey B, Soumelis V. Transcriptome-based identification of novel endotypes in adult atopic dermatitis. Allergy 2022;77:1486-98.
60. Lunjani N, Kerbelker T, Mdletshe FB, Hlela C, O'Mahony L. Phenotypes, endotypes and genotypes of atopic dermatitis and allergy in populations of African ancestry on the continent and diaspora. Front Allergy 2023;4:1203304.
61. Loset M, Brown SJ, Saunes M, Hveem K. Genetics of atopic dermatitis: from DNA sequence to clinical relevance. Dermatology 2019;235:355-64.
62. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-6.
63. Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med 2011;365:1315-27.
64. Virolainen SJ, Satish L, Biagini JM, Chaib H, Chang WC, Dexheimer PJ, et al. Filaggrin loss-of-function variants are associated with atopic dermatitis phenotypes in a diverse, early-life prospective cohort. JCI Insight 2024;9.
65. Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol 2008;121:872-7.e9.

66. Brunner PM, Guttman-Yassky E. Racial differences in atopic dermatitis. Ann Allergy Asthma Immunol 2019;122:449-55.
67. Margolis DJ, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, Campbell LE, et al. The persistence of atopic dermatitis and filaggrin *(FLG)* mutations in a US longitudinal cohort. J Allergy Clin Immunol 2012;130:912-7.
68. Margolis DJ, Gupta J, Apter AJ, Ganguly T, Hoffstad O, Papadopoulos M, et al. Filaggrin-2 variation is associated with more persistent atopic dermatitis in African American subjects. J Allergy Clin Immunol 2014;133:784-9.
69. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat Genet 2015;47:1449-56.
70. Esparza-Gordillo J, Weidinger S, Folster-Holst R, Bauerfeind A, Ruschendorf F, Patone G, et al. A common variant on chromosome 11q13 is associated with atopic dermatitis. Nat Genet 2009;41:596-601.
71. Zhu Y, Mitra N, Feng Y, Tishkoff S, Hoffstad O, Margolis D. *FLG* variation differs between European Americans and African Americans. J Invest Dermatol 2021;141:1855-7.
72. Zhao T, Su Z, Li Y, Zhang X, You Q. Chitinase-3 like–protein-1 function and its role in diseases. Signal Transduct Target Ther 2020;5:201.
73. Dezman K, Korosec P, Rupnik H, Rijavec M. *SPINK5* is associated with early-onset and *CHI3L1* with late-onset atopic dermatitis. Int J Immunogenet 2017;44:212-8.
74. Zhou B, Liang S, Shang S, Li L. Association of *TLR2* and *TLR9* gene polymorphisms with atopic dermatitis: a systematic review and meta-analysis with trial sequential analysis. Immunol Med 2023;46:32-44.
75. Prado-Montes de Oca E, Garcia-Vargas A, Lozano-Inocencio R, Gallegos-Arreola MP, Sandoval-Ramirez L, Davalos-Rodriguez NO, et al. Association of beta-defensin 1 single nucleotide polymorphisms with atopic dermatitis. Int Arch Allergy Immunol 2007;142:211-8.
76. Gao PS, Rafaels NM, Mu D, Hand T, Murray T, Boguniewicz M, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. J Allergy Clin Immunol 2010;125:1403-7.e4.
77. Sugita K. Adipose tissue remodeling via TSLP-mediated IL-4/IL-13 signaling: implications for atopic dermatitis and skin barrier. J Allergy Clin Immunol 2024;154:282-4.
78. Kezic S, O'Regan GM, Lutter R, Jakasa I, Koster ES, Saunders S, et al. Filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines in the stratum corneum of patients with atopic dermatitis and in a murine model of filaggrin deficiency. J Allergy Clin Immunol 2012;129:1031-9.e1.
79. Namkung JH, Lee JE, Kim E, Kim HJ, Seo EY, Jang HY, et al. Association of polymorphisms in genes encoding IL-4, IL-13 and their receptors with atopic dermatitis in a Korean population. Exp Dermatol 2011;20:915-9.
80. He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, et al. Genetic variants of the *IL13* and *IL4* genes and atopic diseases in at-risk children. Genes Immun 2003;4:385-9.
81. Liu X, Nickel R, Beyer K, Wahn U, Ehrlich E, Freidhoff LR, et al. An *IL13* coding region variant is associated with a high total serum IgE level and atopic dermatitis in the German multicenter atopy study (MAS-90). J Allergy Clin Immunol 2000;106:167-70.
82. Deka H, Siddique MA, Ahmed SJ, Mahanta P, Mahanta P. Evaluation of IL-4 and IL-13 single nucleotide polymorphisms and their association with childhood asthma and its severity: a hospital-based case–control study. Cureus 2024;16:e57465.
83. Kim E, Lee JE, Namkung JH, Kim PS, Kim S, Shin ES, et al. Single nucleotide polymorphisms and the haplotype in the *DEFB1* gene are associated with atopic dermatitis in a Korean population. J Dermatol Sci 2009;54:25-30.
84. Peled A, Sarig O, Sun G, Samuelov L, Ma CA, Zhang Y, et al. Loss-of-function mutations in caspase recruitment domain-containing protein 14 *(CARD14)* are associated with a severe variant of atopic dermatitis. J Allergy Clin Immunol 2019;143:173-81.e10.
85. Kim KW, Myers RA, Lee JH, Igartua C, Lee KE, Kim YH, et al. Genome-wide association study of recalcitrant atopic dermatitis in Korean children. J Allergy Clin Immunol 2015;136:678-84.e4.
86. Sliz E, Huilaja L, Pasanen A, Laisk T, Reimann E, Magi R, et al. Uniting biobank resources reveals novel genetic pathways modulating susceptibility for atopic dermatitis. J Allergy Clin Immunol 2022;149:1105-12.e9.
87. Budu-Aggrey A, Kilanowski A, Sobczyk MK, Me Research T, Shringarpure SS, Mitchell R, et al. European and multi-ancestry genome-wide association meta-analysis of atopic dermatitis highlights importance of systemic immune regulation. Nat Commun 2023;14:6172.
88. Kim SH, Yu SY, Choo JH, Kim J, Ahn K, Hwang SY. Epigenetic methylation changes in pregnant women: bisphenol exposure and atopic dermatitis. Int J Mol Sci 2024;25.
89. Jeremian R, Malinowski A, Oh ES, Gooderham M, Sibbald C, Yeung J, et al. Epigenetic and biological age acceleration in children with atopic dermatitis. J Allergy Clin Immunol Glob 2024;3:100275.
90. da Silva Duarte AJ, Sanabani SS. Deciphering epigenetic regulations in the inflammatory pathways of atopic dermatitis. Life Sci 2024;348:122713.
91. Chen C, Zeng J, Lu J. Critical role of epigenetic modification in the pathogenesis of atopic dermatitis. Indian J Dermatol Venereol Leprol 2023;89:700-9.
92. Potaczek DP, Harb H, Michel S, Alhamwe BA, Renz H, Tost J. Epigenetics and allergy: from basic mechanisms to clinical applications. Epigenomics 2017;9:539-71.
93. Baloh CH, Mathias RA. Recent progress in the genetic and epigenetic underpinnings of atopy. J Allergy Clin Immunol 2023;151:60-9.
94. El-Korashi LA, Nafea OE, Nafea AE, Elkholy BM, Elhawy LL, Abdelhadi AA. MicroRNA-155 is a potential predictive tool for atopic dermatitis severity in children: a preliminary study. Egypt J Immunol 2024;31:131-9.
95. Tajima S, Suetake I, Takeshita K, Nakagawa A, Kimura H, Song J. Domain structure of the Dnmt1, Dnmt3a, and Dnmt3b DNA methyltransferases. Adv Exp Med Biol 2022;1389:45-68.
96. Rinaldi L, Datta D, Serrat J, Morey L, Solanas G, Avgustinova A, et al. Dnmt3a and Dnmt3b associate with enhancers to regulate human epidermal stem cell homeostasis. Cell Stem Cell 2016;19:491-501.
97. Sen GL, Reuter JA, Webster DE, Zhu L, Khavari PA. DNMT1 maintains progenitor function in self-renewing somatic tissue. Nature 2010;463:563-7.
98. Akhtar S, Alsayed R, Ahmad F, AlHammadi A, Al-Khawaga S, AlHarami S, et al. Epigenetic control of inflammation in atopic dermatitis. Semin Cell Dev Biol 2024;154:199-207.
99. Kretschmer A, Moller G, Lee H, Laumen H, von Toerne C, Schramm K, et al. A common atopy-associated variant in the Th2 cytokine locus control region impacts transcriptional regulation and alters SMAD3 and SP1 binding. Allergy 2014;69:632-42.
100. Schieck M, Sharma V, Michel S, Toncheva AA, Worth L, Potaczek DP, et al. A polymorphism in the T_H2 locus control region is associated with changes in DNA methylation and gene expression. Allergy 2014;69:1171-80.
101. Ziyab AH, Karmaus W, Holloway JW, Zhang H, Ewart S, Arshad SH. DNA methylation of the filaggrin gene adds to the risk of eczema associated with loss-of-function variants. J Eur Acad Dermatol Venereol 2013;27:e420-3.
102. Schedel M, Leach SM, Strand MJ, Danhorn T, MacBeth M, Faino AV, et al. Molecular networks in atopic mothers impact the risk of infant atopy. Allergy 2023;78:244-57.
103. Sonkoly E, Janson P, Majuri ML, Savinko T, Fyhrquist N, Eidsmo L, et al. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte–associated antigen 4. J Allergy Clin Immunol 2010;126:581-9.e1-20.
104. Zhu Y, Ye F, Fu Y, Zhu X, Wang Z, Wu S, et al. MicroRNA-155-5p regulates the Th1/Th2 cytokines expression and the apoptosis of group 2 innate lymphoid cells via targeting TP53INP1 in allergic rhinitis. Int Immunopharmacol 2021;101:108317.
105. Rebane A, Runnel T, Aab A, Maslovskaja J, Ruckert B, Zimmermann M, et al. MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. J Allergy Clin Immunol 2014;134:836-47.e11.
106. Yang Z, Zeng B, Wang C, Wang H, Huang P, Pan Y. MicroRNA-124 alleviates chronic skin inflammation in atopic eczema via suppressing innate immune responses in keratinocytes. Cell Immunol 2017;319:53-60.
107. Liew WC, Sundaram GM, Quah S, Lum GG, Tan JSL, Ramalingam R, et al. Belinostat resolves skin barrier defects in atopic dermatitis by targeting the dysregulated miR-335:SOX6 axis. J Allergy Clin Immunol 2020;146:606-20.e12.
108. Gu C, Li Y, Wu J, Xu J. IFN-gamma-induced microRNA-29b up-regulation contributes tokeratinocyte apoptosis in atopic dermatitis through inhibiting Bcl2L2. Int J Clin Exp Pathol 2017;10:10117-26.
109. Vaher H, Runnel T, Urgard E, Aab A, Carreras Badosa G, Maslovskaja J, et al. miR-10a-5p is increased in atopic dermatitis and has capacity to inhibit keratinocyte proliferation. Allergy 2019;74:2146-56.
110. Wang J, Huang Y, Wu X, Li D. MicroRNA-939 amplifies *Staphylococcus aureus*–induced matrix metalloproteinase expression in atopic dermatitis. Front Immunol 2024;15:1354154.
111. Bjerre RD, Holm JB, Palleja A, Sølberg J, Skov L, Johansen JD. Skin dysbiosis in the microbiome in atopic dermatitis is site-specific and involves bacteria, fungus and virus. BMC Microbiol 2021;21:256.
112. Han SH, Cheon HI, Hur MS, Kim MJ, Jung WH, Lee YW, et al. Analysis of the skin mycobiome in adult patients with atopic dermatitis. Exp Dermatol 2018;27:366-73.

113. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res 2012;22:850-9.
114. Nekrasova AI, Kalashnikova IG, Bobrova MM, Korobeinikova AV, Bakoev SY, Ashniev GA, et al. Characteristics of the gut microbiota in regard to atopic dermatitis and food allergies of children. Biomedicines 2024;12:553.
115. Paller AS, Kong HH, Seed P, Naik S, Scharschmidt TC, Gallo RL, et al. The microbiome in patients with atopic dermatitis. J Allergy Clin Immunol 2019;143:26-35.
116. Amar Y, Schneider E, Köberle M, Seeholzer T, Musiol S, Hölge Im, et al. Microbial dysbiosis in a mouse model of atopic dermatitis mimics shifts in human microbiome and correlates with the key pro-inflammatory cytokines IL-4, IL-33 and TSLP. J Eur Acad Dermatol Venereol 2022;36:705-16.
117. Zachariassen LF, Krych L, Engkilde K, Nielsen DS, Kot W, Hansen CHF, et al. Sensitivity to oxazolone induced dermatitis is transferable with gut microbiota in mice. Sci Rep 2017;7:44385.
118. Huang K, Li F, Liu Y, Liang B, Qu P, Yang L, et al. Multi-omics analyses reveal interactions between the skin microbiota and skin metabolites in atopic dermatitis. Front Microbiol 2024;15.
119. Kang MJ, Lee SY, Park YM, Kim BS, Lee MJ, Kim JH, et al. Interactions between IL-17 variants and *Streptococcus* in the gut contribute to the development of atopic dermatitis in infancy. Asthma Allergy Immunol Res 2020;13:404-19.
120. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143-55.
121. Grice EA, Segre JA. The skin microbiome. Nat Rev Microbiol 2011;9:244-53.
122. Capone KA, Dowd SE, Stamatas GN, Nikolovski J. Diversity of the human skin microbiome early in life. J Invest Dermatol 2011;131:2026-32.
123. Zhu T, Liu X, Kong FQ, Duan YY, Yee AL, Kim M, et al. Age and mothers: potent influences of children's skin microbiota. J Invest Dermatol 2019;139:2497-505.e6.
124. Clausen ML, Agner T, Lilje B, Edslev SM, Johannesen TB, Andersen PS. Association of disease severity with skin microbiome and filaggrin gene mutations in adult atopic dermatitis. JAMA Dermatol 2018;154:293-300.
125. Severn MM, Horswill AR. *Staphylococcus epidermidis* and its dual lifestyle in skin health and infection. Nat Rev Microbiol 2023;21:97-111.
126. Fyhrquist N, Muirhead G, Prast-Nielsen S, Jeanmougin M, Olah P, Skoog T, et al. Microbe–host interplay in atopic dermatitis and psoriasis. Nat Commun 2019;10:4703.
127. Simpson EL, Villarreal M, Jepson B, Rafaels N, David G, Hanifin J, et al. Patients with atopic dermatitis colonized with *Staphylococcus aureus* have a distinct phenotype and endotype. J Invest Dermatol 2018;138:2224-33.
128. Kenney HM, Yoshida T, Berdyshev E, Calatroni A, Gill SR, Simpson EL, et al. *CERS1* is a biomarker of *Staphylococcus aureus* abundance and atopic dermatitis severity. J Allergy Clin Immunol 2025;155:479-90.
129. Kline SN, Orlando NA, Lee AJ, Wu MJ, Zhang J, Youn C, et al. *Staphylococcus aureus* proteases trigger eosinophil-mediated skin inflammation. Proc Natl Acad Sci U S A 2024;121:e2309243121.
130. Ottman N, Barrientos-Somarribas M, Fyhrquist N, Alexander H, Wisgrill L, Olah P, et al. Microbial and transcriptional differences elucidate atopic dermatitis heterogeneity across skin sites. Allergy 2021;76:1173-87.
131. Lai Y, Cogen AL, Radek KA, Park HJ, Macleod DT, Leichtle A, et al. Activation of TLR2 by a small molecule produced by *Staphylococcus epidermidis* increases antimicrobial defense against bacterial skin infections. J Invest Dermatol 2010;130:2211-21.
132. Volz T, Kaesler S, Draing C, Hartung T, Rocken M, Skabytska Y, et al. Induction of IL-10–balanced immune profiles following exposure to LTA from *Staphylococcus epidermidis*. Exp Dermatol 2018;27:318-26.
133. Faergemann J. Atopic dermatitis and fungi. Clin Microbiol Rev 2002;15:545-63.
134. Schmid B, Künstner A, Fähnrich A, Bersuch E, Schmid-Grendelmeier P, Busch H, et al. Dysbiosis of skin microbiota with increased fungal diversity is associated with severity of disease in atopic dermatitis. J Eur Acad Dermatol Venereol 2022;36:1811-9.
135. Choi Y, Park KY, Han HS, Lee MK, Seo SJ. Comparative analysis of cutaneous fungi in atopic dermatitis patients and healthy individuals. Ann Dermatol 2022;34:118-24.
136. Jagielski T, Rup E, Ziółkowska A, Roeske K, Macura AB, Bielecki J. Distribution of *Malassezia* species on the skin of patients with atopic dermatitis, psoriasis, and healthy volunteers assessed by conventional and molecular identification methods. BMC Dermatol 2014;14:3.
137. Savolainen J, Lammintausta K, Kalimo K, Viander M. *Candida albicans* and atopic dermatitis. Clin Exp Allergy 1993;23:332-9.
138. Storz L, Schmid B, Bosshard PP, Schmid-Grendelmeier P, Bruggen MC, Lang C. Decreased skin colonization with *Malassezia* spp and increased skin colonization with *Candida* spp in patients with severe atopic dermatitis. Front Med (Lausanne) 2024;11:1353784.
139. Hülpüsch C, Rohayem R, Reiger M, Traidl-Hoffmann C. Exploring the skin microbiome in atopic dermatitis pathogenesis and disease modification. J Allergy Clin Immunol 2024;154:31-41.
140. Zhang E, Tanaka T, Tajima M, Tsuboi R, Nishikawa A, Sugita T. Characterization of the skin fungal microbiota in patients with atopic dermatitis and in healthy subjects. Microbiol Immunol 2011;55:625-32.
141. Moosbrugger-Martinz V, Hackl H, Gruber R, Pilecky M, Knabl L, Orth-Höller D, et al. Initial evidence of distinguishable bacterial and fungal dysbiosis in the skin of patients with atopic dermatitis or Netherton syndrome. J Invest Dermatol 2021;141:114-23.
142. Chen YH, Wu CS, Chao YH, Lin CC, Tsai HY, Li YR, et al. *Lactobacillus pentosus* GMNL-77 inhibits skin lesions in imiquimod-induced psoriasis-like mice. J Food Drug Anal 2017;25:559-66.
143. Kim DY, Jung DH, Song EJ, Jang AR, Park JY, Ahn JH, et al. D-Galactose intake alleviates atopic dermatitis in mice by modulating intestinal microbiota. Front Nutr 2022;9:895837.
144. Lee SY, Lee E, Park YM, Hong SJ. Microbiome in the gut–skin axis in atopic dermatitis. Asthma Allergy Immunol Res 2018;10:354-62.
145. Park DH, Kim JW, Park HJ, Hahm DH. Comparative analysis of the microbiome across the gut–skin axis in atopic dermatitis. Int J Mol Sci 2021;22:4228.
146. Song H, Yoo Y, Hwang J, Na YC, Kim HS. *Faecalibacterium prausnitzii* subspecies–level dysbiosis in the human gut microbiome underlying atopic dermatitis. J Allergy Clin Immunol 2016;137:852-60.
147. Watanabe S, Narisawa Y, Arase S, Okamatsu H, Ikenaga T, Tajiri Y, et al. Differences in fecal microflora between patients with atopic dermatitis and healthy control subjects. J Allergy Clin Immunol 2003;111:587-91.
148. Hoskinson C, Medeleanu MV, Reyna ME, Dai DLY, Chowdhury B, Moraes TJ, et al. Antibiotics taken within the first year of life are linked to infant gut microbiome disruption and elevated atopic dermatitis risk. J Allergy Clin Immunol 2024;154:131-42.
149. Akiyama T, Iodi Carstens M, Carstens E. Transmitters and pathways mediating inhibition of spinal itch-signaling neurons by scratching and other counterstimuli. PLoS One 2011;6:e22665.
150. Jin UH, Lee SO, Sridharan G, Lee K, Davidson LA, Jayaraman A, et al. Microbiome-derived tryptophan metabolites and their aryl hydrocarbon receptor-dependent agonist and antagonist activities. Mol Pharmacol 2014;85:777-88.
151. Han CY, Kwon SK, Yeom M, Hahm DH, Park JW, Park HJ, et al. Exploring the differences in the gut microbiome in atopic dermatitis according to the presence of gastrointestinal symptoms. J Clin Med 2022;11:3690.
152. Wang Y, Hou J, Tsui JCC, Wang L, Zhou J, Chan UK, et al. Unique gut microbiome signatures among adult patients with moderate to severe atopic dermatitis in Southern Chinese. Int J Mol Sci 2023;24:12856.
153. Przybilla B, Ring J, Enders F, Winkelmann H. Stigmata of atopic constitution in patients with atopic eczema or atopic respiratory disease. Acta Derm Venereol 1991;71:407-10.
154. Akel M, Barroca C, Blanca A, Huq SO, Ratra D, Shah S, et al. Chronic dermatographic urticaria secondary to systemic lupus erythematosus. Cureus 2024;16:e63109.
155. Liu Z, Wang Y, Wang S, Wu J, Jia C, Tan X, et al. Unraveling the causative connection between urticaria, inflammatory cytokines, and mental disorders: perspectives from genetic evidence. Skin Res Technol 2024;30:e13906.
156. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am 2015;35:161-83.
157. Shah R, Lambert WC, Schwartz RA. Revive the Dennie-Morgan fold: a forgotten sign of atopic dermatitis in children. Acta Dermatovenerol Croat 2023;31:158-9.
158. Tokura Y, Hayano S. Subtypes of atopic dermatitis: from phenotype to endotype. Allergol Int 2022;71:14-24.
159. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387:1109-22.
160. Brunner PM, Israel A, Leonard A, Pavel AB, Kim HJ, Zhang N, et al. Distinct transcriptomic profiles of early-onset atopic dermatitis in blood and skin of pediatric patients. Ann Allergy Asthma Immunol 2019;122:318-30.e3.
161. Brunner PM, Israel A, Zhang N, Leonard A, Wen HC, Huynh T, et al. Early-onset pediatric atopic dermatitis is characterized by $T_H2/T_H17/T_H22$-centered inflammation and lipid alterations. J Allergy Clin Immunol 2018;141:2094-106.
162. Guttman-Yassky E, Diaz A, Pavel AB, Fernandes M, Lefferdink R, Erickson T, et al. Use of tape strips to detect immune and barrier abnormalities in the skin of children with early-onset atopic dermatitis. JAMA Dermatol 2019;155:1358-70.
163. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013;132:1132-8.

164. Dotterud LK, Falk ES. Atopic disease among adults in Northern Russia, an area with heavy air pollution. Acta Derm Venereol 1999;79:448-50.
165. Harrop J, Chinn S, Verlato G, Olivieri M, Norback D, Wjst M, et al. Eczema, atopy and allergen exposure in adults: a population-based study. Clin Exp Allergy 2007;37:526-35.
166. Muto T, Hsieh SD, Sakurai Y, Yoshinaga H, Suto H, Okumura K, et al. Prevalence of atopic dermatitis in Japanese adults. Br J Dermatol 2003;148:117-21.
167. Kawaguchi C, Ozawa M, Hidaka T, Murakami K, Ishikuro M, Ueno F, et al. Skin health survey on atopic dermatitis among Japanese children: the Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study. Allergol Int 2024.
168. Zhou J, Chen H, Zhou S, Liu A, Liang S, Sun X, et al. Trends in atopic dermatitis prevalence among the Chinese population (1990-2021) with projections for 2022-2030. Pediatr Allergy Immunol 2024;35:e14271.
169. Chan LN, Magyari A, Ye M, Al-Alusi NA, Langan SM, Margolis D, et al. The epidemiology of atopic dermatitis in older adults: a population-based study in the United Kingdom. PLoS One 2021;16:e0258219.
170. Zhou L, Leonard A, Pavel AB, Malik K, Raja A, Glickman J, et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2019;144:144-56.
171. He H, Li R, Choi S, Zhou L, Pavel A, Estrada YD, et al. Increased cardiovascular and atherosclerosis markers in blood of older patients with atopic dermatitis. Ann Allergy Asthma Immunol 2020;124:70-8.
172. Mansouri Y, Guttman-Yassky E. Immune pathways in atopic dermatitis, and definition of biomarkers through broad and targeted therapeutics. J Clin Med 2015;4:858-73.
173. Yang L, Fu J, Zhou Y. Research progress in atopic march. Front Immunol 2020;11:1907.
174. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrlander C, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. JAMA Pediatr 2017;171:655-62.
175. Paternoster L, Savenije OEM, Heron J, Evans DM, Vonk JM, Brunekreef B, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. J Allergy Clin Immunol 2018;141:964-71.
176. Belgrave DC, Granell R, Simpson A, Guiver J, Bishop C, Buchan I, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med 2014;11:e1001748.
177. Zeidler C, Raap U, Witte F, Ständer S. Clinical aspects and management of chronic itch. J Allergy Clin Immunol 2023;152:1-10.
178. Yosipovitch G, Kim B, Luger T, Lerner E, Metz M, Adiri R, et al. Similarities and differences in peripheral itch and pain pathways in atopic dermatitis. J Allergy Clin Immunol 2024;153:904-12.
179. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell–dependent itch: involvement of TRPV1 and TRPA1. J Allergy Clin Immunol 2014;133:448-60.
180. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. Nat Immunol 2004;5:752-60.
181. Raap U, Weissmantel S, Gehring M, Eisenberg AM, Kapp A, Folster-Holst R. IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. Pediatr Allergy Immunol 2012;23:285-8.
182. Raap U, Wichmann K, Bruder M, Stander S, Wedi B, Kapp A, et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol 2008;122:421-3.
183. Chovatiya R, Paller AS. JAK inhibitors in the treatment of atopic dermatitis. J Allergy Clin Immunol 2021;148:927-40.
184. Buhl T, Ikoma A, Kempkes C, Cevikbas F, Sulk M, Buddenkotte J, et al. Protease-activated receptor-2 regulates neuro-epidermal communication in atopic dermatitis. Front Immunol 2020;11:1740.
185. Deng L, Costa F, Blake KJ, Choi S, Chandrabalan A, Yousuf MS, et al. *S aureus* drives itch and scratch–induced skin damage through a V8 protease-PAR1 axis. Cell 2023;186:5375-93.e25.
186. Gallo RL, Horswill AR. *Staphylococcus aureus:* the bug behind the itch in atopic dermatitis. J Invest Dermatol 2024;144:950-3.
187. Chu DK, Chu AWL, Rayner DG, Guyatt GH, Yepes-Nuñez JJ, Gomez-Escobar L, et al. Topical treatments for atopic dermatitis (eczema): systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol 2023;152:1493-519.
188. Robinson L, Strowd LC. American Academy of Dermatology guidelines for managing atopic dermatitis. Adv Exp Med Biol 2024;1447:217-25.
189. Bieber T. Atopic dermatitis: an expanding therapeutic pipeline for a complex disease. Nat Rev Drug Discov 2022;21:21-40.
190. Bieber T. Disease modification in inflammatory skin disorders: opportunities and challenges. Nat Rev Drug Discov 2023;22:662-80.
191. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. Dermatology 1993;186:23-31.
192. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 2001;10:11-8.
193. Bakker D, de Bruin-Weller M, Drylewicz J, van Wijk F, Thijs J. Biomarkers in atopic dermatitis. J Allergy Clin Immunol 2023;151:1163-8.
194. Halling AS, Rinnov MR, Ruge IF, Gerner T, Ravn NH, Knudgaard MH, et al. Skin TARC/CCL17 increase precedes the development of childhood atopic dermatitis. J Allergy Clin Immunol 2023;151:1550-7.e6.
195. Morgner B, Tittelbach J, Wiegand C. Induction of psoriasis- and atopic dermatitis–like phenotypes in 3D skin equivalents with a fibroblast-derived matrix. Sci Rep 2023;13:1807.
196. Guttman-Yassky E, Facheris P, Da Rosa JC, Rothenberg-Lausell C, Del Duca E, David E, et al. Oral difelikefalin reduces moderate to severe pruritus and expression of pruritic and inflammatory biomarkers in subjects with atopic dermatitis. J Allergy Clin Immunol 2023;152:916-26.
197. Goleva E. Predicting the future: early-life biomarkers of atopic dermatitis. J Allergy Clin Immunol 2023;151:1479-80.
198. Simpson EL, De Benedetto A, Boguniewicz M, Ong PY, Lussier S, Villarreal M, et al. Phenotypic and endotypic determinants of atopic dermatitis severity from the Atopic Dermatitis Research Network (ADRN) registry. J Allergy Clin Immunol Pract 2023;11:2504-15.
199. He H, Bissonnette R, Wu J, Diaz A, Saint-Cyr Proulx E, Maari C, et al. Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis. J Allergy Clin Immunol 2021;147:199-212.
200. Thijs J, Krastev T, Weidinger S, Buckens CF, de Bruin-Weller M, Bruijnzeel-Koomen C, et al. Biomarkers for atopic dermatitis: a systematic review and meta-analysis. Curr Opin Allergy Clin Immunol 2015;15:453-60.
201. Andersson AM, Solberg J, Koch A, Skov L, Jakasa I, Kezic S, et al. Assessment of biomarkers in pediatric atopic dermatitis by tape strips and skin biopsies. Allergy 2022;77:1499-509.
202. Holm JG, Hurault G, Agner T, Clausen ML, Kezic S, Tanaka RJ, et al. Immunoinflammatory biomarkers in serum are associated with disease severity in atopic dermatitis. Dermatology 2021;237:513-20.
203. Nakahara T, Onozuka D, Nunomura S, Saeki H, Takenaka M, Matsumoto M, et al. The ability of biomarkers to assess the severity of atopic dermatitis. J Allergy Clin Immunol Glob 2024;3:100175.
204. Maintz L, Welchowski T, Herrmann N, Brauer J, Traidl-Hoffmann C, Havenith R, et al. IL-13, periostin and dipeptidyl-peptidase-4 reveal endotype–phenotype associations in atopic dermatitis. Allergy 2023.
205. Meng J, Moriyama M, Feld M, Buddenkotte J, Buhl T, Szollosi A, et al. New mechanism underlying IL-31–induced atopic dermatitis. J Allergy Clin Immunol 2018;141:1677-89.e8.
206. McAleer MA, Jakasa I, Stefanovic N, McLean WHI, Kezic S, Irvine AD. Topical corticosteroids normalize both skin and systemic inflammatory markers in infant atopic dermatitis. Br J Dermatol 2021;185:153-63.
207. Pavel AB, Renert-Yuval Y, Wu J, Del Duca E, Diaz A, Lefferdink R, et al. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. Allergy 2021;76:314-25.
208. McAleer MA, Jakasa I, Hurault G, Sarvari P, McLean WHI, Tanaka RJ, et al. Systemic and stratum corneum biomarkers of severity in infant atopic dermatitis include markers of innate and T helper cell–related immunity and angiogenesis. Br J Dermatol 2019;180:586-96.
209. Sonnenberg-Riethmacher E, Miehe M, Riethmacher D. Periostin in allergy and inflammation. Front Immunol 2021;12:722170.
210. Ungar B, Garcet S, Gonzalez J, Dhingra N, Correa da Rosa J, Shemer A, et al. An integrated model of atopic dermatitis biomarkers highlights the systemic nature of the disease. J Invest Dermatol 2017;137:603-13.
211. Jin S, Park CO, Shin JU, Noh JY, Lee YS, Lee NR, et al. DAMP molecules S100A9 and S100A8 activated by IL-17A and house-dust mites are increased in atopic dermatitis. Exp Dermatol 2014;23:938-41.
212. Andersson AM, Ingham AC, Edslev SM, Sølberg J, Skov L, Koch A, et al. Ethnic endotypes in paediatric atopic dermatitis depend on immunotype, lipid composition and microbiota of the skin. J Eur Acad Dermatol Venereol 2024;38:365-74.
213. Hashimoto T, Yokozeki H, Karasuyama H, Satoh T. IL-31–generating network in atopic dermatitis comprising macrophages, basophils, thymic stromal lymphopoietin, and periostin. J Allergy Clin Immunol 2023;151:737-46.e6.
214. Jeong H, Lee N, Uhm C, Cho K, Oh H, Oh Y, et al. RAB25 coordinates filaggrin-containing keratohyalin granule maturation and affects atopic dermatitis severity. Allergy 2023;78:1007-19.
215. Kozera E, Flora A, Stewart T, Gill K, Xu J, De La Vega MA, et al. Dupilumab-associated head and neck dermatitis resolves temporarily with itraconazole therapy and rapidly with transition to upadacitinib, with *Malassezia*-specific

immunoglobulin E levels mirroring clinical response. J Am Acad Dermatol 2023; 88:255-7.
216. Myles IA, Castillo CR, Barbian KD, Kanakabandi K, Virtaneva K, Fitzmeyer E, et al. Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair. Sci Transl Med 2020;12.
217. Nakatsuji T, Hata TR, Tong Y, Cheng JY, Shafiq F, Butcher AM, et al. Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial. Nat Med 2021;27:700-9.
218. Weiss A, Delavenne E, Matias C, Lagler H, Simon D, Li P, et al. Topical niclosamide (ATx201) reduces *Staphylococcus aureus* colonization and increases Shannon diversity of the skin microbiome in atopic dermatitis patients in a randomized, double-blind, placebo-controlled phase 2 trial. Clin Transl Med 2022; 12:e790.
219. Ehst BD, Strober B, Blauvelt A, Maslin D, Macaro D, Carpenter N, et al. A randomized, double-blinded, phase 2 trial of EDP1815, an oral immunomodulatory preparation of *Prevotella histicola,* in adults with mild-to-moderate plaque psoriasis. Front Med (Lausanne) 2024;11:1292406.
220. Mitamura Y, Nunomura S, Nanri Y, Ogawa M, Yoshihara T, Masuoka M, et al. The IL-13/periostin/IL-24 pathway causes epidermal barrier dysfunction in allergic skin inflammation. Allergy 2018;73:1881-91.
221. Marinho A, Nunes C, Reis S. Hyaluronic acid: a key ingredient in the therapy of inflammation. Biomolecules 2021;11.
222. Evrard C, Faway E, De Vuyst E, Svensek O, De Glas V, Bergerat D, et al. Deletion of *TNFAIP6* gene in human keratinocytes demonstrates a role for TSG-6 to retain hyaluronan inside epidermis. JID Innov 2021;1:100054.
223. Menzies-Gow A, Ponnarambil S, Downie J, Bowen K, Hellqvist A, Colice G. DESTINATION: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21:279.
224. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. J Am Acad Dermatol 2019;80:1013-21.
225. Chen YL, Gutowska-Owsiak D, Hardman CS, Westmoreland M, MacKenzie T, Cifuentes L, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. Sci Transl Med 2019;11.
226. Simpson EL, Guttman-Yassky E, Pawlikowski J, Ghorayeb EG, Ota T, Lebwohl MG. Interleukin-1alpha inhibitor bermekimab in patients with atopic dermatitis: randomized and nonrandomized studies. Arch Dermatol Res 2024;316:589.
227. Liu H, Archer NK, Dillen CA, Wang Y, Ashbaugh AG, Ortines RV, et al. *Staphylococcus aureus* epicutaneous exposure drives skin inflammation via IL-36–mediated T cell responses. Cell Host Microbe 2017;22:653-66.e5.
228. Bissonnette R, Abramovits W, Saint-Cyr Proulx E, Lee P, Guttman-Yassky E, Zovko E, et al. Spesolimab, an anti–interleukin-36 receptor antibody, in patients with moderate-to-severe atopic dermatitis: results from a multicentre, randomized, double-blind, placebo-controlled, phase IIa study. J Eur Acad Dermatol Venereol 2023;37:549-57.
229. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. J Am Acad Dermatol 2019;80:89-98.e3.
230. Simpson EL, Schlievert PM, Yoshida T, Lussier S, Boguniewicz M, Hata T, et al. Rapid reduction in *Staphylococcus aureus* in atopic dermatitis subjects following dupilumab treatment. J Allergy Clin Immunol 2023;152:1179-95.
231. Clabbers J, Boesjes C, Spekhorst L, van Gisbergen MW, Maas E, Marshall J, et al. Influence of pathogenic filaggrin variants on dupilumab treatment in atopic dermatitis. J Allergy Clin Immunol 2024;153:1155-61.e4.
232. Bieber T. In search of the Holy Grail in atopic dermatitis: will dupilumab become the first disease-modifying atopic dermatitis drug? J Allergy Clin Immunol 2023; 151:694-6.
233. Beck LA, Muraro A, Boguniewicz M, Chen Z, Zahn J, Rodríguez Marco A. Dupilumab reduces inflammatory biomarkers in pediatric patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2025;155:135-43.
234. Ratchataswan T, Banzon TM, Thyssen JP, Weidinger S, Guttman-Yassky E, Phipatanakul W. Biologics for treatment of atopic dermatitis: current status and future prospect. J Allergy Clin Immunol Pract 2021;9:1053-65.
235. O'Kane D, Davis L, Ardern-Jones M, Laws P, Shaw L, Cork M, et al. Treatment outcomes of patients with atopic dermatitis (AD) treated with dupilumab through the Early Access to Medicines Scheme (EAMS) in the UK. Ulster Med J 2021;90:70-6.
236. Butala S, Paller AS. Biologics in the management of childhood atopic dermatitis. J Allergy Clin Immunol 2023;151:681-5.
237. Bernardo D, Bieber T, Torres T. Lebrikizumab for the treatment of moderate-to-severe atopic dermatitis. Am J Clin Dermatol 2023;24:753-64.
238. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A, et al. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. N Engl J Med 2023;388:1080-91.
239. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti–IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005;60:693-6.
240. Niebuhr M, Scharonow H, Gathmann M, Mamerow D, Werfel T. Staphylococcal exotoxins are strong inducers of IL-22: a potential role in atopic dermatitis. J Allergy Clin Immunol 2010;126:1176-83.e4.
241. Gutowska-Owsiak D, Schaupp AL, Salimi M, Taylor S, Ogg GS. Interleukin-22 downregulates filaggrin expression and affects expression of profilaggrin processing enzymes. Br J Dermatol 2011;165:492-8.
242. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. J Am Acad Dermatol 2018;78:872-81.e6.
243. Lee GR, Lee DE, Shi VY. Emerging targeted treatments. In: Chan LS, Shi VY, editors. Atopic dermatitis: inside out or outside in. New Delhi: Elsevier; 2023. pp. 237-51.
244. Ungar B, Pavel AB, Li R, Kimmel G, Nia J, Hashim P, et al. Phase 2 randomized, double-blind study of IL-17 targeting with secukinumab in atopic dermatitis. J Allergy Clin Immunol 2021;147:394-7.
245. Zundell MP, Gottlieb AB, Stanger R. Atopic dermatitis as a paradoxical reaction to secukinumab in a patient with plaque psoriasis. J Drugs Dermatol 2024;23:97-9.
246. Tyring SK, Rich P, Tada Y, Beeck S, Messina I, Liu J, et al. Risankizumab in patients with moderate-to-severe atopic dermatitis: a phase 2, randomized, double-blind, placebo-controlled study. Dermatol Ther (Heidelb) 2023;13:595-608.
247. Bissonnette R, DuBois J, Facheris P, Del Duca E, Kim M, Correa Da Rosa J, et al. Clinical and molecular effects of oral CCR4 antagonist RPT193 in atopic dermatitis: a phase 1 study. Allergy 2024;79:924-36.
248. Ruzicka T, Mihara R. Anti–interleukin-31 receptor A antibody for atopic dermatitis. N Engl J Med 2017;376:2093.
249. Stein Gold L, Bissonnette R, Forman S, Zaenglein A, Kuo Y, Angel B, et al. A maximum-use trial of ruxolitinib cream in children aged 2-11 years with moderate to severe atopic dermatitis. Am J Clin Dermatol 2025;26:275-89.
250. Hoy SM. Correction to: Baricitinib: a review in moderate to severe atopic dermatitis. Am J Clin Dermatol 2022;23:747.
251. Thyssen JP, Halling AS, Schmid-Grendelmeier P, Guttman-Yassky E, Silverberg JI. Comorbidities of atopic dermatitis—what does the evidence say? J Allergy Clin Immunol 2023;151:1155-62.
252. Gewiss C, Augustin M. Recent insights into comorbidities in atopic dermatitis. Expert Rev Clin Immunol 2023;19:393-404.
253. Biagini JM, Kroner JW, Baatyrbek Kyzy A, Gonzales A, He H, Stevens M, et al. Longitudinal atopic dermatitis endotypes: an atopic march paradigm that includes Black children. J Allergy Clin Immunol 2022;149:1702-10.e4.
254. Zhao SS, Yiu ZZN. Genetically proxied IL-6 receptor inhibition is associated with increased risk of atopic dermatitis. J Allergy Clin Immunol 2024;154:666-9.
255. Huffaker MF, Kanchan K, Bahnson HT, Ruczinski I, Shankar G, Leung DYM, et al. Epidermal differentiation complex genetic variation in atopic dermatitis and peanut allergy. J Allergy Clin Immunol 2023;151:1137-42.e4.
256. Chennareddy S, Brunner PM. From genes to geography: mapping allergic disease landscapes with spatial transcriptomics. J Allergy Clin Immunol 2025;155:800-2.

REFERENCES

E1. Luger T, Chu CY, Elgendy A, Ibrahim S, Murashkin N, Ranjan S, et al. Pimecrolimus 1% cream for mild-to-moderate atopic dermatitis: a systematic review and meta-analysis with a focus on children and sensitive skin areas. Eur J Dermatol 2023;33:474-86.
E2. Dhar S, De A, Saha A, Chitnis KR, Mane A, Dhoot D, et al. Intermittent or sequential topical tacrolimus in atopic dermatitis: systematic review and meta-analysis. Cureus 2023;15:e50640.
E3. Kim K, Kim M, Rhee E, Lee MH, Yang HJ, Park S, et al. Efficacy and safety of low-dose cyclosporine relative to immunomodulatory drugs used in atopic dermatitis: a systematic review and meta-analysis. J Clin Med 2023;12:1390.
E4. Caron AGM, Bloem M, El Khattabi H, de Waal AC, van Huizen AM, Denswil NP, et al. The wide variety of methotrexate dosing regimens for the treatment of atopic dermatitis: a systematic review. J Dermatolog Treat 2024;35:2292962.
E5. Bracho-Borro M, Franco-Ruiz PA, Magana M. The use of azathioprine in atopic dermatitis: a review. Dermatol Ther 2022;35:e15665.
E6. Meggitt SJ, Reynolds NJ. Azathioprine for atopic dermatitis. Clin Exp Dermatol 2001;26:369-75.
E7. Phan K, Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. J Dermatolog Treat 2020;31:810-4.
E8. Bissonnette R, DuBois J, Facheris P, Del Duca E, Kim M, Correa Da Rosa J, et al. Clinical and molecular effects of oral CCR4 antagonist RPT193 in atopic dermatitis: a phase 1 study. Allergy 2024;79:924-36.
E9. O'Kane D, Davis L, Ardern-Jones M, Laws P, Shaw L, Cork M, et al. Treatment outcomes of patients with atopic dermatitis (AD) treated with dupilumab through the Early Access to Medicines Scheme (EAMS) in the UK. Ulster Med J 2021;90:70-6.
E10. Beck LA, Muraro A, Boguniewicz M, Chen Z, Zahn J, Rodríguez Marco A. Dupilumab reduces inflammatory biomarkers in pediatric patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol 2025;155:135-43.
E11. Russo F, Cioppa V, Lazzeri L, Milanesi N, Galluzzo M, D'Erme AM, et al. Evaluating the clinical meaning of dermatology life quality index scores between different phenotypes of atopic dermatitis in patients before and after biologic therapy with dupilumab. Dermatitis 2024.
E12. Pereyra-Rodriguez JJ, Herranz P, Ruiz-Villaverde R, Elosua-Gonzalez M, Galan-Gutierrez M, Figueras-Nart I, et al. Treatment of severe atopic dermatitis with tralokinumab in clinical practice: short-term effectiveness and safety results. Clin Exp Dermatol 2023;48:991-7.
E13. Pezzolo E, Gambardella A, Guanti M, Bianchelli T, Bertoldi A, Giacchetti A, et al. Tralokinumab shows clinical improvement in patients with prurigo nodularis–like phenotype atopic dermatitis: a multicenter, prospective, open-label case series study. J Am Acad Dermatol 2023;89:430-2.
E14. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016;75:494-503.
E15. Silverberg JI, Guttman-Yassky E, Gontijo Lima R. Lebrikizumab for moderate-to-severe atopic dermatitis. Reply. N Engl J Med 2023;388:2299-300.
E16. Bernardo D, Bieber T, Torres T. Lebrikizumab for the treatment of moderate-to-severe atopic dermatitis. Am J Clin Dermatol 2023;24:753-64.
E17. Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti–IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy 2005;60:693-6.
E18. Whetstone CE, Cusack RP, Price E, Howie K, Stevens C, Al-Sajee D, et al. Effect of benralizumab on inflammation in skin after intradermal allergen challenge in patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol Glob 2024;3:100310.
E19. Brunner PM, Pavel AB, Khattri S, Leonard A, Malik K, Rose S, et al. Baseline IL-22 expression in patients with atopic dermatitis stratifies tissue responses to fezakinumab. J Allergy Clin Immunol 2019;143:142-54.
E20. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. J Am Acad Dermatol 2018;78:872-81.e6.
E21. Ungar B, Pavel AB, Li R, Kimmel G, Nia J, Hashim P, et al. Phase 2 randomized, double-blind study of IL-17 targeting with secukinumab in atopic dermatitis. J Allergy Clin Immunol 2021;147:394-7.
E22. Zundell MP, Gottlieb AB, Stanger R. Atopic dermatitis as a paradoxical reaction to secukinumab in a patient with plaque psoriasis. J Drugs Dermatol 2024;23:97-9.
E23. Husein-ElAhmed H, Steinhoff M. Effectiveness of ustekinumab in patients with atopic dermatitis: analysis of real-world evidence. J Dermatolog Treat 2022;33:1838-43.
E24. Saeki H, Kabashima K, Tokura Y, Murata Y, Shiraishi A, Tamamura R, et al. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. Br J Dermatol 2017;177:419-27.
E25. Tyring SK, Rich P, Tada Y, Beeck S, Messina I, Liu J, et al. Risankizumab in patients with moderate-to-severe atopic dermatitis: a phase 2, randomized, double-blind, placebo-controlled study. Dermatol Ther (Heidelb) 2023;13:595-608.
E26. Amatore F, Connell E, Aymonier M, Gaudy-Marqueste C, Richard MA. Mogamulizumab in a patient with Sezary syndrome and severe atopic dermatitis. Eur J Cancer 2019;156:((suppl 1):2021S51-2.
E27. Chen YL, Gutowska-Owsiak D, Hardman CS, Westmoreland M, MacKenzie T, Cifuentes L, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. Sci Transl Med 2019;11:eaax2945. https://pubmed.ncbi.nlm.nih.gov/31645451/.
E28. Silverberg JI, Boguniewicz M, Quintana FJ, Clark RA, Gross L, Hirano I, et al. Tapinarof validates the aryl hydrocarbon receptor as a therapeutic target: a clinical review. J Allergy Clin Immunol 2024;154:1-10.
E29. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. J Am Acad Dermatol 2019;80:89-98.e3.
E30. Menzies-Gow A, Ponnarambil S, Downie J, Bowen K, Hellqvist A, Colice G. DESTINATION: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res 2020;21:279.
E31. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. J Am Acad Dermatol 2019;80:1013-21.
E32. Gauvreau GM, Hohlfeld JM, FitzGerald JM, Boulet LP, Cockcroft DW, Davis BE, et al. Inhaled anti-TSLP antibody fragment, ecleralimab, blocks responses to allergen in mild asthma. Eur Respir J 2023;61:2201193.
E33. Simpson EL, Guttman-Yassky E, Pawlikowski J, Ghorayeb EG, Ota T, Lebwohl MG. Interleukin-1alpha inhibitor bermekimab in patients with atopic dermatitis: randomized and nonrandomized studies. Arch Dermatol Res 2024;316:589.
E34. Bissonnette R, Abramovits W, Saint-Cyr Proulx E, Lee P, Guttman-Yassky E, Zovko E, et al. Spesolimab, an anti–interleukin-36 receptor antibody, in patients with moderate-to-severe atopic dermatitis: results from a multicentre, randomized, double-blind, placebo-controlled, phase IIa study. J Eur Acad Dermatol Venereol 2023;37:549-57.
E35. Kozera E, Flora A, Stewart T, Gill K, Xu J, De La Vega MA, et al. Dupilumab-associated head and neck dermatitis resolves temporarily with itraconazole therapy and rapidly with transition to upadacitinib, with *Malassezia*-specific immunoglobulin E levels mirroring clinical response. J Am Acad Dermatol 2023;88:255-7.
E36. Guttman-Yassky E, Thyssen JP, Silverberg JI, Papp KA, Paller AS, Weidinger S, et al. Safety of upadacitinib in moderate-to-severe atopic dermatitis: an integrated analysis of phase 3 studies. J Allergy Clin Immunol 2023;151:172-81.
E37. Gargiulo L, Ibba L, Alfano A, Malagoli P, Amoruso F, Balato A, et al. Short-term effectiveness and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis: results from a 16-week real-world multicenter retrospective study—il AD (Italian landscape atopic dermatitis). J Dermatolog Treat 2024;35:2411855.
E38. Napolitano M, Potestio L, Pezzolo E, Rossi M, Saboya R, Galli B, et al. Efficacy of abrocitinib and baricitinib on "difficult-to-treat areas" in patients with atopic dermatitis: a multicentre study. Clin Exp Dermatol 2024 Oct 9llae415.
E39. Napolitano M, Fornaro L, Potestio L, Fabbrocini G, Patruno C. Abrocitinib in atopic dermatitis: review of the current literature and clinical trials. Drugs Today (Barc) 2022;58:373-87.
E40. Zhou C, Yang X, Yang B, Yan G, Dong X, Ding Y, et al. A randomized, double-blind, placebo-controlled phase II study to evaluate the efficacy and safety of ivarmacitinib (SHR0302) in adult patients with moderate-to-severe alopecia areata. J Am Acad Dermatol 2023;89:911-9.
E41. Zhao Y, Zhang L, Ding Y, Tao X, Ji C, Dong X, et al. Efficacy and safety of SHR0302, a highly selective Janus kinase 1 inhibitor, in patients with moderate to severe atopic dermatitis: a phase II randomized clinical trial. Am J Clin Dermatol 2021;22:877-89.
E42. Hoy SM. Correction to: Baricitinib: a review in moderate to severe atopic dermatitis. Am J Clin Dermatol 2022;23:747.
E43. Stein Gold L, Bissonnette R, Forman S, Zaenglein A, Kuo Y, Angel B, et al. A maximum-use trial of ruxolitinib cream in children aged 2-11 years with moderate to severe atopic dermatitis. Am J Clin Dermatol 2025;26:275-89.
E44. Landis MN, Arya M, Smith S, Draelos Z, Usdan L, Tarabar S, et al. Efficacy and safety of topical brepocitinib for the treatment of mild-to-moderate atopic dermatitis: a phase IIb, randomized, double-blind, vehicle-controlled, dose-ranging and parallel-group study. Br J Dermatol 2022;187:878-87.

E45. Changelian P, Xu C, Mnich S, Hope H, Kostecki K, Hirsch J, et al. ATI-1777, a topical Jak1/3 inhibitor, may benefit atopic dermatitis without systemic drug exposure: results from preclinical development and phase 2a randomized control study ATI-1777-AD-201. JID Innov 2024;4:100251.
E46. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, et al. Delgocitinib ointment in pediatric patients with atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. J Am Acad Dermatol 2021;85:854-62.
E47. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled /study and an open-label, long-term extension study. J Am Acad Dermatol 2020;82:823-31.
E48. Thoma G, Duthaler RO, Waelchli R, Hauchard A, Bruno S, Strittmatter-Keller U, et al. Discovery and characterization of the topical soft JAK inhibitor CEE321 for atopic dermatitis. J Med Chem 2023;66:2161-8.
E49. Zhang Y, Zhou H, Jiang Z, Wu D, Zhuang J, Li W, et al. Efficacy, safety, and survival findings after long-term follow-up of ZGJAK002: a phase 2 study comparing jaktinib at 100 mg twice daily (BID) and 200 mg once daily (QD) in patients with myelofibrosis. Am J Hematol 2024; 99:774-9.
E50. Piscitelli SC, Pavel AB, McHale K, Jett JE, Collins J, Gillmor D, et al. A phase 1b, randomized, single-center trial of topical cerdulatinib (DMVT-502) in patients with mild-to-moderate atopic dermatitis. J Invest Dermatol 2021;141: 1847-51.

TABLE E1. Medication for AD

Name	Type	Target	Mechanism	Used	Suggested for:	Study
Pimecrolimus	Small synthetic molecule	Calcineurin	Inhibition of calcineurin, which disrupts transcription of IL-2 and T-cell activation	AD	Mild to moderate AD	E1
Tacrolimus	Small natural molecule	Calcineurin	Inhibition of calcineurin, which disrupts transcription of IL-2 and T-cell activation	AD	Moderate to severe AD	E2
Ciclosporin/ cyclosporine	Small natural molecule	Calcineurin	Inhibition of calcineurin, which disrupts transcription of IL-2 and T-cell activation	AD	Severe, refractory AD	E3
Crisaborole	Small natural molecule	PDE4	PDE4 inhibitor	AD	Mild to moderate AD	E14
Methotrexate	Small natural molecule	Dihydrofolate reductase	Prevents reduction of dihydrobiopterin to tetrahydrobiopterin, leading to NO synthase uncoupling and increased apoptosis of T cells	AD	Moderate to severe AD	E4
Azathioprine	Small natural molecule	GTPase Rac1	Antagonizes purine metabolism, inhibits DNA, RNA and protein synthesis	RA, AD	Moderate to severe AD	E5, E6
Mycophenolate mofetil	Small natural molecule	Inosine-5-monophosphate	Inhibits inosine-5′-monophosphate dehydrogenase, depleting guanosine nucleotides in T and B cells, inhibiting their proliferation, and suppressing immune response and antibody formation	AD, transplant rejection	Moderate to severe AD	E7
RPT193	Small synthetic molecule	CCR4	Binds to CCR4, may block, eg, chemokine-mediated migration and proliferation of T_H2 cells		Moderate to severe AD	E8
Dupilumab	Humanized mAb ($IgG_4\kappa$)	IL4Ra	Binds to IL-4R, inhibits *IL4* and *IL13* signaling	AD	Moderate to severe AD	E9-E11
Tralokinumab	Humanized mAb ($IgG_4\lambda$)	IL13	Binds to IL-13 with high affinity, inhibiting its interaction with receptors	AD	Moderate to severe AD	E12, E13
Lebrikizumab	Humanized mAb ($IgG_4\kappa$)	IL13	Binds to IL-13 with high affinity, prevents IL-4Ra/IL13Ra1 heterodimerization	AD	Moderate to severe AD	E15, E16
Mepolizumab	Humanized mAb ($IgG_1\kappa$)	IL5	Antagonizes IL-5 reducing eosinophil levels	AD	Eosinophilia-driven AD	E17
Benralizumab	Humanized mAb ($IgG_1\kappa$)	IL5Rα	Binds to IL-5R with high affinity, blocks its signaling	AD	Eosinophilia-driven AD	E18
Fezakinumab	Humanized mAb ($IgG_1\lambda$)	IL22	Binds IL-22, preventing formation of IL-22/IL-22 receptor complex	AD, RA	Moderate to severe AD	E19, E20
Ixekinumab	Humanized mAb ($IgG_4\kappa$)	IL17A	Selectively binds to IL-17A, preventing its binding to IL-17R	AD, PSO, RA	Moderate to severe AD (T_H17 dominant)	
Secukinumab	Humanized mAb ($IgG_1\kappa$)	IL17A	Selectively binds to IL-17A, preventing IL17-A interaction with IL-17 receptor	PSO	Moderate to severe AD (T_H17 dominant)	E21, E22
Ustekinumab	Humanized mAb ($IgG_1\kappa$)	p40	Binds p40 subunit of IL-12 and IL-23, preventing their interaction with their receptor	PSO, CD		E23, E24
Risankizumab	Humanized mAb ($IgG_1\kappa$)	p19	Binds to p19 subunit of IL-23, inhibiting IL-23 from interacting with IL-23R	PSO, CD	Moderate to severe AD	E25

(Continued)

TABLE E1. *(Continued)*

Name	Type	Target	Mechanism	Used	Suggested for:	Study
Mogamulizumab	Humanized mAb ($IgG_1\kappa$)	CCR4	Binds to CCR4, may block, eg, chemokine-mediated migration and proliferation of T_H2 cells	Cutaneous T-cell lymphoma, tumors	Being studied for moderate to severe AD	E26
Etokimab	Humanized mAb ($IgG_1\kappa$)	IL33	Binds to IL33 and prevents especially activation of T_H2-associated inflammatory pathway	AD, asthma, chronic rhinosinusitis	Moderate to severe AD	E27
Tapinarof	Small natural molecule	AhR	Binds to and activates AhR, inducing gene expression, resulting in downregulation of proinflammatory mediators	AD, PSO	Mild to moderate AD	E28, E29
Tezepelumab	Humanized mAb ($IgG_2\lambda$)	TSLP	Blocks TSLP by preventing interaction with its receptor complex	Asthma	AD with severe inflammation	E30, E31
Ecleralimab	Humanized Fab-G_1-$\lambda2$	TSLP	Inhaled anti-TSLP antibody, binds TSLP, prevents TSLP receptor activation	Asthma	Being studied for moderate to severe AD	E32
Bermekimab	Humanized mAb ($IgG_1\kappa$)	IL1A	Binds to IL1A, reduces inflammation	AD, hidradenitis suppurativa	Moderate to severe AD	E33
Spesolimab	Humanized mAb ($IgG_1\kappa$)	IL36R	Binds to IL36R, reduces inflammation	AD, CD, PSO, UC	Moderate to severe AD	E34
Upadacitinib	Small synthetic molecule	JAK1	Selective JAK1 inhibitor	AD, RA, SLE, CD	Moderate to severe AD	E35, E36
Abrocintinib	Small synthetic molecule	JAK1	Selective JAK1 inhibitor	AD, type 1 diabetes mellitus	Moderate to severe AD	E37-E39
Ivarmacitinib	Small synthetic molecule	JAK1	Selective JAK1 inhibitor	AD, RA, UC	Under clinical development for AD	E40, E41
Baricitinib	Small synthetic molecule	JAK1/JAK2	Binds to JAK1 and JAK2 with high affinity, prevents activation of STATs	AD, RA		E38, E42
Ruxolitinib	Small synthetic molecule	JAK1/JAK2	Binds to JAK1 and JAK2 with high affinity, prevents activation of STATs	AD	Topical treatment for mild to moderate AD	E43
Brepocitinib	Small synthetic molecule	JAK1/TYK2	Binds to JAK1 and TYK2 with high affinity, prevents activation of STATs	AD, CD, PSO	Under development for AD	E44
ATI-1777	Small synthetic molecule	JAK1/JAK3	Binds to JAK1 and JAK3 with high affinity, prevents activation of STATs		Being studied for moderate to severe AD	E45
Delgocitinib	Small synthetic molecule	Pan-JAKi	Blocks multiple JAK enzymes simultaneously to reduce T_H1/T_H17, T_H2 inflammation	AD, chronic hand eczema	Topical treatment for AD	E46, E47
CEE312	Small synthetic molecule	Pan-JAKi	Blocks multiple JAK enzymes simultaneously to reduce T_H1/T_H17, T_H2 inflammation		Under early-stage research for AD	E48
Jaktinib	Small synthetic molecule	Pan-JAKi	Blocks multiple JAK enzymes simultaneously to reduce T_H1/T_H17, T_H2 inflammation		In development for inflammatory diseases	E49
Cerdulatinib	Small synthetic molecule	Pan-JAKi	Blocks multiple JAK enzymes simultaneously to reduce T_H1/T_H17, T_H2 inflammation		Being studied for inflammatory skin diseases	E50

CD, Crohn disease; *JAKi,* JAK inhibitor; *mAb,* monoclonal antibody; *PSO,* psoriasis; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus; *TYK2,* tyrosine kinase 2; *UC,* ulcerative colitis.