

Atopic dermatitis

Stephan Weidinger^{1*}, Lisa A. Beck², Thomas Bieber^{3,4}, Kenji Kabashima⁵
and Alan D. Irvine^{6,7,8*}

Abstract | Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, with a lifetime prevalence of up to 20% and substantial effects on quality of life. AD is characterized by intense itch, recurrent eczematous lesions and a fluctuating course. AD has a strong heritability component and is closely related to and commonly co-occurs with other atopic diseases (such as asthma and allergic rhinitis). Several pathophysiological mechanisms contribute to AD aetiology and clinical manifestations. Impairment of epidermal barrier function, for example, owing to deficiency in the structural protein filaggrin, can promote inflammation and T cell infiltration. The immune response in AD is skewed towards T helper 2 cell-mediated pathways and can in turn favour epidermal barrier disruption. Other contributing factors to AD onset include dysbiosis of the skin microbiota (in particular overgrowth of *Staphylococcus aureus*), systemic immune responses (including immunoglobulin E (IgE)-mediated sensitization) and neuroinflammation, which is involved in itch. Current treatments for AD include topical moisturizers and anti-inflammatory agents (such as corticosteroids, calcineurin inhibitors and cAMP-specific 3',5'-cyclic phosphodiesterase 4 (PDE4) inhibitors), phototherapy and systemic immunosuppressants. Translational research has fostered the development of targeted small molecules and biologic therapies, especially for moderate-to-severe disease.

Atopic dermatitis (AD), also known as atopic eczema, is the most common inflammatory skin disorder in the developed world, with a lifetime prevalence of 15–20% in developed countries¹. The condition most often develops during childhood and is characterized by recurrent eczematous lesions (that is, poorly defined, erythematous (red) patches with exudation, blistering and crusting at early stages and scaling, fissuring (cracking) and lichenification (thickening) at later stages) and intense itch and discomfort. These manifestations can lead to sleep loss, diminished self-esteem and poor performance at school and work. AD is an extremely heterogeneous disease with a wide spectrum of clinical features ranging from minimal flexural (in body folds) eczema to erythroderma (erythema (redness) affecting >90% of the body surface that can lead to skin cracking) to eczema limited to the hands, and AD presumably encompasses a variety of subtypes with distinct and overlapping pathological mechanisms.

Since the early 2000s, the pathophysiological concepts underlying AD have shifted from models that held type 1 hypersensitivity-mediated (that is, immunoglobulin E (IgE)-mediated immune response) allergies and atopy (BOX 1), exaggerated T helper 2 (T_H2) cell-mediated immune responses and epidermal barrier deficiency as key drivers towards an integrated view, in which varying degrees of epidermal barrier disruption, activation

of different T cell subsets and dysbiosis (imbalance) of the commensal skin microbiota interact and contribute to cause the varying clinical presentations. AD is strongly associated with atopic comorbidities such as asthma, allergic rhinitis and food allergies, but the mechanistic link between these diseases is insufficiently understood (BOX 1). AD is also associated with an increased risk of other inflammatory diseases, such as arthritis and inflammatory bowel disease, and often causes psychological disturbances². AD confers a substantial burden to patients and their families and causes high health-care costs worldwide. Reflecting the heterogeneity of the disease and uncertainties about the pathogenesis, a confusing terminology has developed, with terms such as (atopic) eczema, AD and childhood eczema used synonymously in the literature. Similarly, multiple sets of diagnostic criteria, outcomes and measurement tools have been proposed, but only few have adequate validity, reliability or ease of use. The need for harmonization has stimulated consensus projects such as the global multi-stakeholder Harmonizing Outcome Measures for Eczema (HOME) initiative³. Currently, licensed treatment options are limited, but insights from molecular and clinical research are now increasingly being translated into new AD clinical trials and the approval of new treatments.

In this Primer, we review current knowledge of the epidemiology and clinical features of AD. We discuss

*e-mail: sweidinger@dermatology.uni-kiel.de;
irvinea@tcd.ie
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Author addresses

¹Department of Dermatology and Allergy, University Hospital Schleswig-Holstein, Kiel, Germany.

²Department of Dermatology, Medicine and Pathology, University of Rochester Medical Center, Rochester, NY, USA.

³Department of Dermatology and Allergy, University of Bonn, Bonn, Germany.

⁴The Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland.

⁵Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

⁶Paediatric Dermatology, Our Lady's Children's Hospital Crumlin, Dublin, Ireland.

⁷National Children's Research Centre, Crumlin, Dublin, Ireland.

⁸Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

established therapies and review current understanding of the pathophysiology of AD and how this understanding is driving new, targeted therapies.

Epidemiology

The clinical heterogeneity of AD makes it challenging to accurately measure its frequency; nevertheless, evidence suggests that it is one of the most common chronic diseases worldwide. AD was originally regarded as a disease of early childhood (affecting children of <7 years of age), with prevalence up to 25%, but more-recent evidence shows that AD is also very prevalent in adults, with rates of 7–10%^{1,4,5}. Data from the WHO Global Burden of Diseases initiative indicate that at least 230 million people worldwide have AD (global annual period prevalence 3.5%; [Global Health Data Exchange](#); accessed 1 October 2017), and AD is the leading cause of the non-fatal disease burden of skin conditions⁶. Lifetime prevalence is >15% in many countries, particularly in affluent settings¹.

AD can manifest at any point in life, but the incidence peaks in infancy, with an onset before 6 years of age in an estimated 80% of patients⁷. After initiation, the course can be continuous for many years but can also show a relapsing-remitting nature⁸. Early birth cohort studies had suggested that the disease clears in >50% of affected children, but these studies were limited by inadequate sample sizes and/or length of follow-up⁴. More-recent cross-sectional studies show 1-year prevalences of ~10%, and a meta-analysis of 7 birth cohort studies with follow-up times of up to 26 years found no substantial difference in AD prevalence before and after childhood and annual prevalences of up to 14.6% in adults⁴ in developed countries. Thus, the proportion of patients with persistent or adult-onset disease or with relapses after long asymptomatic intervals is much higher than previously thought, and AD is a lifelong disease with variable phenotypic expression^{5,9}.

Although no reliable estimates of the incidence of AD are available, the International Study of Asthma and Allergies in Childhood (ISAAC) provides robust period prevalence trend data. This study measured reported symptoms of AD in children of 6–7 years of age and adolescents of 13–14 years of age across multiple countries

using uniform and validated questionnaires at 2 time points that were 5–10 years apart¹⁰ (FIG. 1). The ISAAC showed that AD prevalence varies substantially in different areas of the world, even between highly genetically similar populations (such as individuals of the same ethnicity), suggesting that environmental factors are also important determinants of disease expression. The prevalences of AD symptoms in children of 6–7 years of age increased over time in most geographical areas, particularly in low-income countries (especially in Africa and southeast Asia). By contrast, the prevalences in children of ≥12 years of age overall remained stable at ~20% (FIG. 1). On the basis of these observations, it has been suggested that the maximum prevalence is reached when adverse environmental conditions, probably related to industrialization and a Western lifestyle, lead to disease manifestation in predisposed individuals¹¹.

Risk factors

The strongest known risk factor for AD is a family history of atopic diseases, in particular AD. The presence of any atopic disease in one parent is estimated to increase a child's risk of developing AD 1.5-fold, whereas the risk is increased ~3-fold and ~5-fold, respectively, if one or both parents have AD^{12,13}. Although multiple environmental risk factors have been proposed, few are supported by strong epidemiological data, and effect sizes are generally small. The best established risk factors are living in an urban setting and in regions with low ultraviolet light exposure or dry climatic conditions, consuming a diet high in sugars and polyunsaturated fatty acids (typical of Western countries), repeated exposure to antibiotics before 5 years of age, a small family size and high household education level¹⁴. By contrast, the data are inconsistent on the effects of maternal or postnatal tobacco exposure, long-term exclusive breastfeeding, routine childhood vaccinations, viral or bacterial infections, air pollutants, farm environments and household hair-bearing pets^{14,15}.

Findings from environmental epidemiology are often interpreted as indirect support for the so-called 'hygiene hypothesis', which postulates that reduced or altered early-life microbial exposures, owing to changes in environment and hygiene practices, cause a dysbalanced maturation of the immune system and thereby increase the risk of developing allergic and inflammatory diseases. However, most studies that tested the hygiene hypothesis used the development of atopy (BOX 1) rather than specific atopic diseases as the readout, and there is increasing recognition that the concept of atopy is probably an oversimplification of complex host–environment interactions and could even be counterproductive from a public health standpoint¹⁶.

Comorbidities

Many patients with AD, in particular those with severe disease, show IgE-mediated sensitization to common allergens¹⁷. A high proportion (~37%) of infants and toddlers with AD also have food allergy, and the prevalence of food allergy in the adult population with AD is ~10%¹⁸. In early infancy, IgE responses are usually directed against food allergens, and a subset of infants with AD and

IgE-mediated reactions to food also have true food allergy with immediate-type IgE-mediated non-eczematous reactions and/or delayed exacerbations of AD. However, such delayed eczematous exacerbations of AD are difficult to attribute to a reaction to food with certainty, and their true prevalence and importance are still unclear, as is their mechanism¹⁹. Food allergies to hen's egg and cow's milk typically resolve during childhood, whereas peanut allergy tends to persist²⁰ (BOX 2).

Sensitization to inhaled allergens occurs mostly after infancy and can cause AD flares upon exposure²¹. The most common comorbidities of AD are allergic rhinitis and asthma, which co-occur in up to one-quarter to one-third of patients^{5,22,23}. However, twin and sibship studies as well as genetic association studies indicate that this increased risk of comorbid atopic conditions is largely attributable to shared inherited susceptibility factors rather than IgE-mediated sensitization or shared environmental factors^{24,25}.

AD is also associated with several non-atopic comorbid conditions, in particular mental health disorders and other autoimmune-mediated or immune-mediated diseases. Robust evidence shows that children and adolescents with AD are at increased risk of developing mental health disorders, in particular attention-deficit/hyperactivity disorder, depression, anxiety, conduct disorder and autism, and this relationship is further exacerbated by sleep disturbance and disease severity^{26,27}. Adults with AD develop depression and anxiety more commonly than healthy adults^{28,29}. AD is weakly associated with inflammatory bowel disease and rheumatoid arthritis^{30,31} as well as alopecia areata and vitiligo^{32,33}. A systematic review indicated a modest association of severe AD with cutaneous T cell lymphoma, which could be inflated by the heterogeneity in AD assessment

tools between studies and potential misclassification of AD as cutaneous T cell lymphoma³⁴. By contrast, the risk of type 1 diabetes mellitus and certain malignancies such as glioma, meningioma and acute lymphoblastic leukaemia seems to be decreased in AD³⁰. The skewed type 2 immune response that is characteristic of most patients with AD could inhibit the T_H17 cell dysregulation that is typical of autoimmunity in general and of type 1 diabetes mellitus specifically³⁵. High-quality epidemiological studies have shown conflicting signals regarding the link between AD and cardiovascular and metabolic diseases^{36–39}.

Mechanisms/pathophysiology

AD is a heterogeneous disease that is thought to be triggered by environmental factors in genetically susceptible individuals. Both gene–gene and gene–environment effects are thought to explain the underlying pathological mechanisms of epidermal barrier abnormalities and T cell-driven skin inflammation. Dysbiosis of the skin microbiota could also have a role in AD pathogenesis, and the relative and temporal influences of all these mechanisms could explain the clinical heterogeneity observed among patients with AD⁴⁰ (FIG. 2).

Genetic susceptibility

The strongest AD risk factor is a positive family history of atopic diseases, especially AD¹². Twin studies suggest a heritability of ~75%, which might be an overestimation owing to methodological weaknesses of these studies⁴¹. Association studies, in particular those using genome-wide or targeted high-throughput approaches, have identified 34 specific genomic regions that probably harbour one or more genetic variants associated with AD susceptibility^{42–48} (TABLE 1). AD loci are enriched for genes that might contribute to immune abnormalities, in particular innate immune signalling and T cell activation as well as T_H2 cell differentiation. Only a few true causal genes and their molecular mechanisms have been elucidated. Altogether, these genetic AD susceptibility loci account for <20% of the total heritability⁴⁷. This observation could be explained by the marked heterogeneity of the phenotype, the cumulative effects of multiple genetic variations and the existence of gene–gene and/or gene–environment interactions, structural variation of the genome and heritable epigenetic mechanisms.

FLG. The strongest known genetic risk factor for AD is semi-dominant null mutations in *FLG*, which encodes the epidermal protein filaggrin, that lead to a reduction in filaggrin expression⁴⁹ (BOX 3). *FLG* mutations primarily cause ichthyosis vulgaris, a semi-dominant cornification disorder in which abnormal keratinocyte differentiation results in dry, scaling and thickened skin⁴⁹. Approximately 10% of individuals of European and Japanese descent carry a single loss-of-function mutation within *FLG* exon 3 that results in a truncated profilaggrin molecule that cannot be cleaved into filaggrin monomers. These individuals have a mild expression of ichthyosis, such as generalized skin dryness and a subtle palmar hyperlinearity (exaggerated line markings on the palms) and are at an ~threefold

Box 1 | Atopy and the atopic march

The concept of atopy has troubled clinicians and scientists since the term was introduced in 1923 to describe an 'inherited human hypersensitiveness' (REF.²⁰³). Today, atopy commonly refers to a tendency to produce immunoglobulin E (IgE) antibodies in response to harmless environmental antigens and to develop symptoms typical of atopic diseases, that is, asthma, allergic rhinitis (inflammation of the nasal mucosa, with or without conjunctivitis (inflammation of conjunctiva, the thin layer that covers the white part of the eye)), food allergy or atopic dermatitis (AD)²⁰⁴. Although atopic diseases often co-occur in the same individual and cluster in families, ~20–30% of patients with AD, in particular those with mild disease, do not show signs of IgE-mediated sensitization or have comorbid asthma or rhinitis¹⁷. This observation has led to much debate as well as confusion in terminology and the interchangeable use of the terms AD, atopic eczema and eczema. Currently, most evidence suggests that IgE-mediated sensitization is a secondary phenomenon that can amplify existing inflammatory lesions^{205–208}, a hypothesis that might also explain why anti-IgE therapy and anti-histamine H1 receptor therapies show little efficacy in AD^{209,210}. Similarly, there is much debate about the concept of an 'atopic march', which is based on the age-associated incidence peaks of atopic diseases and postulates a predictable and sequential series of overlapping phenotypes ranging from AD and food allergy to asthma, and subsequently allergic rhinitis, in susceptible individuals. The longitudinal nature of the atopic march concept has been challenged by cohort studies, which suggested that the association between asthma and AD can occur much earlier than previously thought (that is, early wheeze can co-occur with or even precede skin symptoms²¹¹), that only a small fraction of children with AD have a disease course consistent with an atopic march²¹² and that IgE-mediated sensitization is not the major shared mechanism driving the excess comorbidity of atopic diseases²⁴.

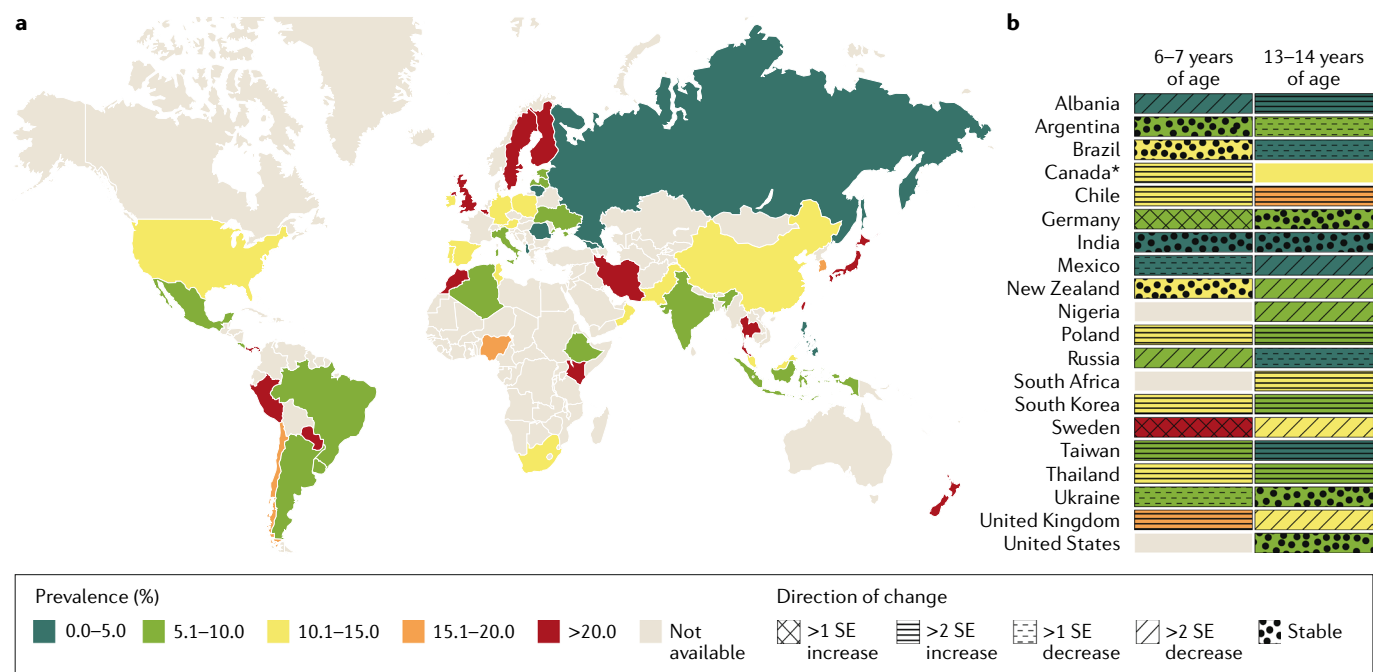


Fig. 1 | **Global prevalence of atopic dermatitis symptoms.** **a** | Parental report of lifetime prevalence of atopic dermatitis (AD) in children of 13–14 years of age based on data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase III. **b** | Parental report of 1-year prevalence of AD symptoms in children of 6–7 and 13–14 years of age in 2000–2001 (ISAAC phase III) in selected countries, as well as the direction of change compared with 1994–1995 data (ISAAC phase I). The ISAAC assessed the prevalence of AD symptoms at two time points; the first was based on reports collected between 1992 and 1998, and the second was based on reports dated between 1999 and 2004. The direction of change in the prevalence between the two time points is expressed as a multiple of the standard error (SE) of the average value at the first time point. In children of 13–14 years of age, the prevalence of AD symptoms seemed to have stabilized at ~20% in most countries, with the exception of the United Kingdom, New Zealand and Sweden, which had formerly had high rates that are now slightly decreased¹⁰, although the factors mediating these reductions are poorly understood. However, rates are lower but continue to increase in younger children and in particular in low-income countries. *Data not from the ISAAC. Data from REF.¹⁰.

increased risk to develop AD⁴⁹. However, only ~20% of patients with mild-to-moderate AD carry *FLG* mutations^{50,51}, and >50% of individuals carrying *FLG* mutations do not develop any atopic disease⁵¹, indicating that *FLG* mutations are neither necessary nor sufficient to cause AD and that yet unknown additional factors are needed to drive full AD manifestation.

An increased skin permeability to exogenous substances has been proposed as the most plausible mechanism linking filaggrin deficiency and AD, but studies using skin equivalents (in vitro models of human skin, with fibroblasts and keratinocytes and occasionally immune cells)⁵² and animal models^{53,54} have investigated only low molecular mass tracers and have delivered conflicting results. A proteomic study on skin equivalents has demonstrated that the mechanisms downstream of filaggrin deficiency are complex and probably involve a dysregulation of multiple other proteins relevant for inflammatory, proteolytic and cytoskeletal functions⁵². In addition, there are three *FLG* variant alleles in the general population, encoding profilaggrin proteins comprising 10, 11 or 12 repeats that can, therefore, generate 10, 11 or 12 filaggrin monomers⁵⁵. Thus, these copy number variants further influence the amount of filaggrin in the stratum corneum and can also influence the risk of AD.

Other genes. Another locus robustly associated with AD and other atopic diseases is the T_H2 cytokine cluster on chromosome 5q31.1, where the genes encoding the canonical cytokines of type 2 immunity, IL-4 and IL-13, are clustered with the constitutively expressed DNA repair gene *RAD50* (REFS^{56,57}). The locus displays a complex linkage disequilibrium pattern and seems to harbour multiple independent signals of association between AD phenotype and genetic variants, including *RAD50*. These association signals are genetic variants that are only risk markers and do not necessarily have a causative role. *RAD50* has no known function directly related to AD, but its 3' end is part of a locus control region that, through epigenetic remodelling, regulates the expression of the surrounding type 2 immunity cytokine genes⁵⁸; preliminary evidence indicates that gene variants in this locus control region interact with epigenetic mechanisms to skew adaptive immune response patterns towards a type 2 phenotype⁵⁹ (BOX 4).

On chromosome 11q13.5, low-frequency functional variants in the *LRRC32* coding sequence cause a decreased expression of glycoprotein A repetitions predominant (GARP; also known as leucine-rich repeat-containing protein 32), a transmembrane cell surface receptor that binds latent transforming growth factor- β (TGF β). This reduced GARP expression could

Box 2 | Atopic dermatitis and food allergy

A close relationship between atopic dermatitis (AD) and food allergy, especially in childhood, is well established. AD is a major risk factor for food allergy in infancy and early childhood²⁰. Infants with severe AD, early-onset AD and a longer duration of AD have a much higher risk of food allergy. The most common allergens are peanut, hen's egg and cow's milk, but other allergens are gaining importance, including sesame. By contrast, it is much less common for food allergy to precede AD onset, although this sequence has been noted in a small number of children²¹³. Intervention trials in children with established AD who are at high risk of food allergy have shown that early oral introduction of potentially allergenic foods can prevent the development of allergy in many children²¹⁴. These studies and other lines of evidence, such as the association of inherited skin barrier deficits and peanut allergy²¹⁵ and experiments in mouse models, suggested the dual exposure to allergen ('twin allergen') hypothesis. This hypothesis states that percutaneous exposure to an allergen and subsequent sensitization is crucial for the development of allergy, whereas oral sensitization is tolerogenic, that is, it induces tolerance of the immune system towards that specific allergen²¹³.

potentially impair the interaction of T regulatory cells with circulating latent TGF β (REF. 60).

Epidermal barrier dysfunction

The epidermal barrier dysfunction observed in patients with AD can be mediated through primary mechanisms, such as *FLG* mutations, and/or secondary mechanisms, for example, the itch-scratch cycle (see below) or the reduced expression of epidermal structural proteins or lipids observed in response to type 2 immunity cytokines such as IL-4, IL-13 and IL-33 (REFS^{61,62}). Several epidermal changes have been observed in both affected and non-lesional (that is, apparently healthy) skin of patients with AD, such as increased pH (REF. 63), reduced water retention^{63,64}, easy irritability⁶⁵, increased permeability to low molecular mass chemicals⁶⁶ and increased susceptibility to infection^{67,68}. At the molecular level, a reduced expression of epidermal differentiation-related structural proteins⁶⁹, imbalances in protease-protease inhibitor interactions^{70,71}, an altered composition and lamellar organization of epidermal lipids^{72,73}, reduced expression of tight junction proteins^{74,75} and an altered surface microbiota colonization pattern, with a greater abundance of *Staphylococcus aureus*⁷⁶, have been observed in both lesional and non-lesional skin sites (FIG. 2).

Epidermal barrier disruption promotes inflammation through dysregulation of immunomodulatory proteins⁵² and the release of damage-associated molecular pattern molecules, including alarmins such as IL-1 β , IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). Alarmins are a diverse group of proteins that are released in response to tissue damage and induce inflammation^{77,78}. The most widely established cause for impairment of the epidermal barrier is an inherited filaggrin deficiency (BOX 3), which also leads to upregulation of pro-inflammatory cytokines expression⁷⁹; the combination of inflammation and barrier impairment

leads to increased percutaneous allergen (antigen) priming⁸⁰. Conversely, an inflammatory response can in turn trigger epidermal barrier disruption and reduced expression of proteins of the stratum corneum and tight junctions^{77,81}. Interestingly, inflammation could also be responsible for the cutaneous manifestations observed in monogenic immunodeficiency disorders, such as dedicator of cytokinesis protein 8 (DOCK8) deficiency syndrome⁸², in which IL-31 overexpression causes severe itch and scratching⁸³, and Wiskott-Aldrich syndrome⁸⁴.

Cutaneous inflammation

AD lesions typically show a cellular infiltrate that mainly consists of CD4⁺ T cells, which are considered the key drivers of inflammation, as well as an increased number of various dendritic cell subsets including Langerhans cells (resident dendritic cells of the skin and mucosa), probably owing to enhanced antigen presentation. The number of activated Langerhans cells, with elongation of dendrites penetrating intact tight junctions for antigen uptake, is increased in AD lesions but not in healthy or non-lesional AD skin⁷⁵. However, non-lesional skin shows immunohistological changes, including spongiosis (intercellular oedema (abnormal accumulation of fluid)) and T cell infiltrations, that are analogous, albeit more-subtle, to those found in lesional skin⁸⁵. Furthermore, the expression of genes encoding proteins involved in maintaining epidermal barrier integrity was decreased and the expression of T_H cell genes was increased in both diseased and non-lesional skin⁸⁶ (FIG. 2). In lesions, the expression of a much larger number of genes, mostly related to keratinocyte activity and T cell infiltration, was altered; in particular genes encoding T_H2 cell-associated (IL-4, IL-10 and IL-13) and T_H22 cell-associated (IL-22) proteins were upregulated⁸⁵. The role and activation of T_H1 cell-mediated and T_H17 cell-mediated responses is yet unclear, but the associated cytokines seem to be overexpressed in chronic disease stages and in particular in children and people of Asian descent^{61,85,87}. One study further postulated that in AD there is a disease stage-dependent progressive upregulation of T_H2, T_H17 and T_H22 cytokines from non-lesional skin through acute and chronic lesions⁸⁵.

The release of alarmins triggered by epithelial barrier disruption activates inflammatory dendritic epidermal cells and initiates T_H2 cell-mediated responses. Activated T_H2 cells release IL-4 and IL-13, which, among other effects, promote B cell IgE class switching and production of antigen-specific IgE molecules via the signal transducer and activator of transcription (STAT) pathway⁸⁸ (FIG. 3). The antigen specificity of the skin-infiltrating T cells in AD remains insufficiently understood. Most patients with AD have increased IgE-mediated reactivity towards aeroallergens, food proteins, microbial antigens and/or keratinocyte-derived auto-antigens^{89–91}. Indeed, exposure to allergens can contribute to AD flares in IgE-sensitized patients²¹, and antigen-specific T cell clones that recognize allergens⁹², microbial antigens⁹³ and autoantigens^{93,94} have been cloned from lesional AD skin. However, the proportion of such T cells in chronic lesions is very low, and a T cell receptor (TCR) β chain-sequencing study indicated that the T cell infiltrates in both non-lesional and lesional AD skin are highly polyclonal⁹⁵.

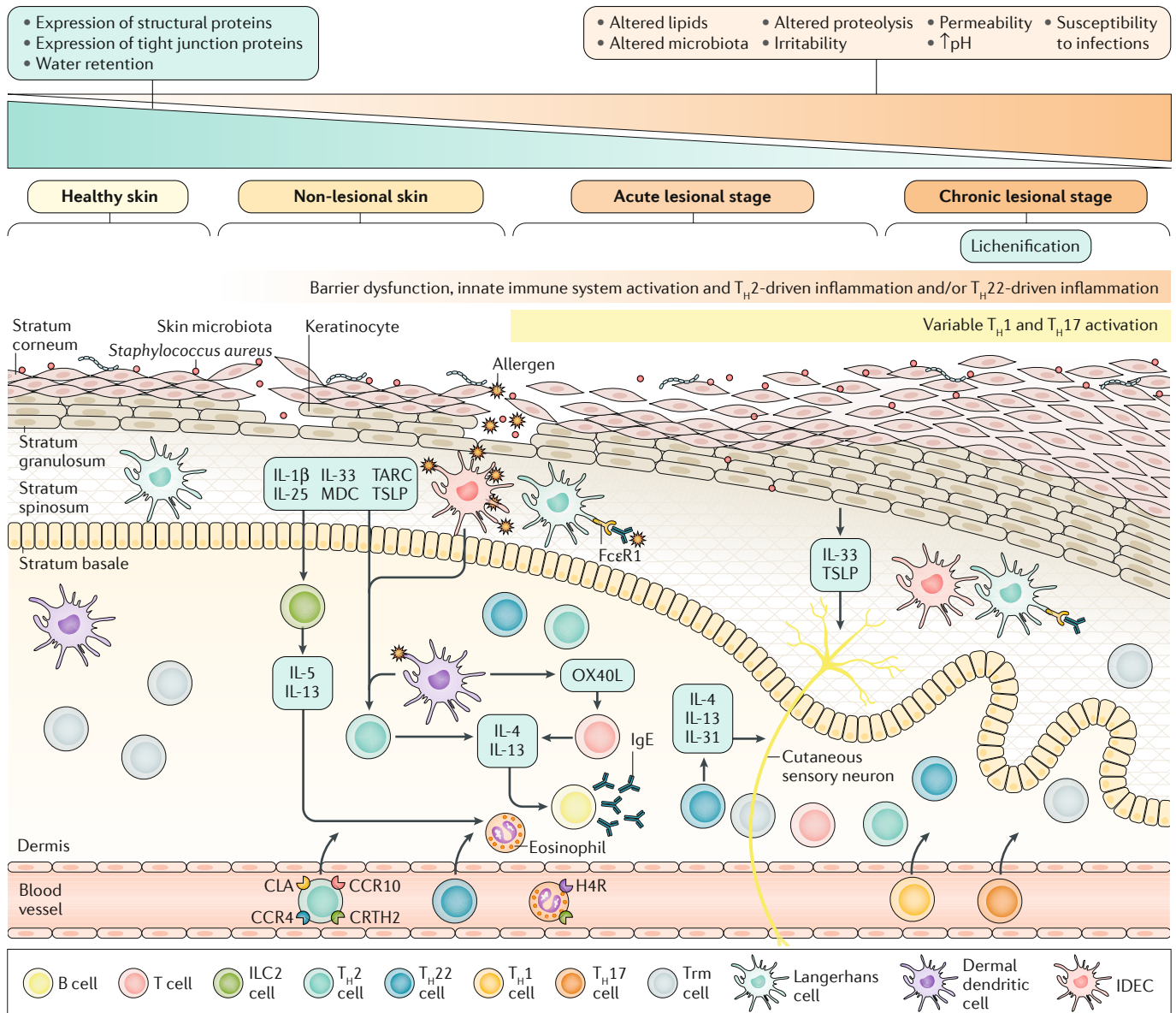


Fig. 2 | Stage-based pathogenesis and main mechanisms of atopic dermatitis. Epidermal barrier disruption stimulates keratinocytes to express chemokines such as thymus and activation-regulated chemokine (TARC; also known as CC-chemokine ligand 17 (CCL17)) and macrophage-derived chemokine (MDC; also known as CCL22)²¹⁶, as well as innate immune cytokines such as IL-1 β , IL-33 and thymic stromal lymphopoietin (TSLP). These mediators expand and activate skin-resident group 2 innate lymphoid cells (ILC2s) and T helper 2 (T_H2) cell-mediated immune responses^{217,218}. TSLP induces the expression by dendritic cells of OX40 ligand (OX40L; also known as tumour necrosis factor ligand superfamily member 4 (TNFSF4)), which binds to OX40L receptor present on naive T cells and stimulates the production of IL-4, IL-5 and IL-13 (REF.²¹⁹). Inflammatory dendritic epidermal cells (IDECs) as well as dermal dendritic cells take up exogenous antigens and self-antigens released from damaged cells and promote type 2 immunity. CD8⁺ T cells producing type 2 immunity cytokines infiltrate atopic dermatitis (AD) skin²²⁰, and activated T_H2 cells release IL-4 and IL-13, which promote immunoglobulin E (IgE) class switching (a change in the immunoglobulin class produced by B cells). ILC2s are a potent source of IL-5 and IL-13 (REFS^{217,221,222}) and can further amplify type 2 immunity²¹⁷ and as a consequence IgE production^{222,223}. Infiltrating T cells in AD express

various skin-homing adhesion molecules, such as the cutaneous lymphocyte antigen (CLA), a glycan moiety that includes P-selectin glycoprotein ligand 1, as well as chemokine (CC-chemokine receptor 4 (CCR4) and CCR10) and lipid (chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2; also known as prostaglandin D2 receptor 2)) chemoattractant receptors²²⁴. Eosinophils expressing CRTH2 and histamine H4 receptor (H4R) are also recruited to lesional skin. Preliminary evidence shows that antigen-primed T cells can also remain as local pools of T resident memory (Trm) cells, enabling rapid recall responses^{92,225}. In contrast to healthy skin, the skin of individuals with AD has increased numbers of dendritic cell subtypes, including Langerhans cells, expressing high-affinity immunoglobulin- ϵ receptors (Fc ϵ R1s). IgE antibodies bound to dendritic cells by Fc ϵ R1 can facilitate the uptake of allergens and initiate T cell-mediated type 4 (delayed type) hypersensitivity reactions²²⁶. IL-33, TSLP and the downstream T_H2 cytokines¹⁰³ directly communicate with cutaneous sensory neurons to exacerbate pruritus^{101,227}, highlighting the dynamic interaction between barrier dysfunction, type 2 immunity and itch perception. In chronic disease stages, a mixed T cell infiltrate and possible autoimmune mechanisms perpetuate skin inflammation and promote cutaneous remodelling and neuroinflammation.

Neuroimmune interactions

Itch is induced by a variety of pruritogens (antigens, molecular mediators such as histamine and other substances inducing pruritus, that is, itch) and mediated by cutaneous pruriceptive primary sensory nerves (slow-conducting, non-myelinated C fibres and fast myelinated A δ fibres); these nerves transmit the pruritic signal via afferent fibres to the spinal cord⁹⁶ (FIG. 3). In animal models of AD skin, sprouting, density and thickness of epidermal neurons is increased^{97,98}, a finding that could explain the characteristic skin pruritus produced by innocuous mechanical stimulation. Such hyperinnervation is probably caused by an imbalance between nerve elongation factors (such as nerve growth factor and IL-31) and nerve repulsion factors (such as semaphorin 3A). Artemin, a glial cell-derived neurotrophic factor, is produced by fibroblasts and keratinocytes and induces abnormal peripheral innervation and thermal hyperalgesia (increased sensitivity to pain)⁸⁴. Air pollutants act on aryl hydrocarbon receptor on keratinocytes to produce artemin, leading to epidermal hyperinnervation and hypersensitivity to pruritus⁹⁹. All these neuroimmune interactions can be exacerbated by psychological stress¹⁰⁰.

The best studied pruritogen is histamine, which typically is released from mast cells and basophils in the context of a type 1 hypersensitivity reaction; histamine activates a subset of sensory neurons that express histamine H1 receptor (H1R) and H4R and transient receptor potential cation channel subfamily A member 1 (TRPV1)⁹⁶. In AD, in addition to histamine, the increased expression of other pruritogens, such as endothelin 1 (ET1), which activates TRPV1, and TSLP^{101,102}, as well as type 2 cytokines such as IL-4, IL-13 and IL-31 and signalling via histamine-independent molecular pathways¹⁰¹, could be more important than histamine for the induction of itch. In particular, TSLP released by keratinocytes directly activates sensory neurons expressing transient receptor potential cation channel subfamily A member 1 (TRPA1)¹⁰¹, and type 2 cytokines directly stimulate afferent neurons via IL-4 receptor subunit- α (IL-4R α) and Janus kinase 1 (JAK1)¹⁰³ (FIG. 3). This observation can explain why dupilumab, an anti-IL-4R α monoclonal antibody, not only reduced tissue inflammation and AD signs but also rapidly improved itch symptoms in AD^{104,105}. IL-31 released by several type 2 immunity cells in skin lesions mediates itch by stimulating neurons expressing IL-31 receptor subunit- α (IL-31R α) or TRPV1 or TRPA1 (REF.¹⁰⁶) and increases neurite (neuronal process) branching in the skin⁹⁷. In a phase II trial, nemolizumab, a humanized monoclonal anti-IL-31R α antibody, significantly improved pruritus in patients with AD; however, the effect of nemolizumab on AD signs was only modest, suggesting that IL-31 does not have an upstream role in AD pathogenesis¹⁰⁷.

The role of the microbiota

The skin of patients with AD has substantial microbial abnormalities; whether these alterations are primary, that is, causative of AD, or secondary to epidermal barrier disruption and T_H2 cell-skewed immunity is still uncertain. *S. aureus* is commonly found on the skin of patients

with AD, with reported prevalence varying from 30% to 100% depending on the age of the patient, the severity of AD, the sample size and sampling and analysis methods to detect *S. aureus*, whereas in healthy controls, the prevalence is ~20%^{108,109}. A meta-analysis of 95 observational studies that used culture-based methods reported that the prevalence of *S. aureus* in patients with AD was 70% on lesional skin and 39% on non-lesional skin or healthy skin¹⁰⁹ within the same patient. The prevalence was related to disease severity¹⁰⁹, a finding that was confirmed in real-time PCR studies¹⁰⁸. The prevalence of the various species within the microbiota was altered across diverse body sites, which was most pronounced at sites of predilection (such as the popliteal fossa (depression at the back of the knee joint) and antecubital fossa (depression on the anterior surface of the elbow joint)) and in inflamed skin¹¹⁰, and microbial diversity was reduced during an AD flare. Microbiota diversity decreased in inflamed AD skin in favour of members of the genus *Staphylococcus* and *S. aureus* in particular⁷⁶, and in patients with AD, during a severe flare, the composition of *Staphylococcus* spp. within the microbiota could be reduced to a single strain of *S. aureus*¹¹¹. The microbiota composition reverted to the pre-flare composition during treatment and recovery⁷⁶.

One of the functions of the normal skin microbiota is suppression of *S. aureus* growth; birth cohort studies have shown that the presence of *Staphylococcus* spp. other than *S. aureus* at day 2 of life might protect infants against later development of AD¹¹². *S. aureus* expresses numerous virulence factors that have proven roles in the pathogenesis of both superficial and invasive infections; several virulence factors contribute to AD pathogenesis or disease exacerbation through mechanisms acting on keratinocytes and immune cells, both in vitro and in human skin biopsy samples and in murine allergy models¹¹³. In addition to the well-characterized role of *S. aureus* in AD, other organisms, including yeasts, probably have substantial roles, for example, *Malassezia* (previously known as *Pityrosporum*) spp., which can directly stimulate skin inflammation¹¹⁴.

Diagnosis, screening and prevention

Clinical phenotype

The clinical phenotype observed in individuals with AD is highly variable and is at least in part related to age, ethnicity and disease severity¹¹⁵. The clinical diagnosis is usually easy to make but can be difficult in infants and toddlers and in elderly people, in whom the clinical features could be more atypical (BOX 5). Especially in adults, skin biopsies can help to exclude malignant diseases such as cutaneous T cell lymphoma. To support diagnosis, several sets of criteria have been developed. The Hanifin and Rajka criteria and the American Academy of Dermatology Consensus Criteria both distinguish so-called essential, common and associated features and can be useful in the clinical setting¹¹⁵.

The essential features according to the two classification criteria referenced above are intense itch; acute, subacute or chronic eczematous lesions; and a chronic or relapsing disease course. AD lesions can occur on any body part, although they typically show an age-related distribution

Table 1 | Susceptibility loci and most plausible candidate gene(s) associated with atopic dermatitis

Susceptibility locus	Most credible candidate gene(s)	Known or proposed function(s)
Cytokine-mediated signalling		
2q12.1	<i>IL1RL1</i>	Subunit of the IL-33 receptor; involved in T _H cell function
	<i>IL18R1</i>	Subunits of the IL-18 receptor; involved in regulation of inflammatory response via NF-κB
	<i>IL18RAP</i>	
3p22.3	<i>CCR4</i>	CC-chemokine receptor; involved in leukocyte trafficking
5p13.2	<i>IL7R</i>	Subunit of the IL-7 and TSLP receptors; involved in proliferation of lymphoid progenitors, release of T cell-attracting chemokines and promotion of T _H 2 cell response
5q22.1	<i>TSLP</i>	Involved in release of T cell-attracting chemokines, promotion of T _H 2 cell response and antimicrobial peptide activity in the oral cavity and on the skin
10p15.1	<i>IL15RA</i>	IL-15 receptor subunit; involved in proliferation and stimulation of different lymphocytes
	<i>IL2RA</i>	IL-2 receptor subunit; involved in proliferation and stimulation of different lymphocytes
17q21.2	<i>STAT3</i>	Involved in signal transduction, transcription activation and mediation of cellular responses to interleukins
20q13.33	<i>TNFRSF6B</i>	TNF receptor superfamily member; involved in protection against apoptosis
Leukocyte differentiation		
1q21.3	<i>IL6R</i>	Subunit of the IL-6 receptor; involved in differentiation of multiple immune cells, especially B cells
4q27	<i>IL2</i>	Involved in differentiation, proliferation and activation of multiple immune cells (T cells, B cells, macrophages and natural killer cells)
	<i>IL21</i>	
5q31.1	<i>IL4</i>	Mainly produced by activated T _H 2 cells; involved in B cell proliferation and IgE isotype switching
	<i>IL13</i>	
7p22.2	<i>CARD11</i>	Involved in TCR-mediated T cell activation and NF-κB activation
11q13.5	<i>LRRC32</i>	Involved in regulation of T regulatory cell function and TGFβ activation
14q13.2	<i>PPP2R3C</i>	Involved in regulation of protein phosphatases and activation-induced cell death of B cells
Transcription regulation		
1q21.2	<i>CIART</i>	Involved in circadian transcriptional repression
8q21.13	<i>ZBTB10</i>	Involved in transcription regulation
9p21.3	<i>DMRTA1</i>	Involved in transcription regulation
17q21.32-q21.33	<i>ZNF652</i>	Involved in transcription regulation
Structural molecule activity		
1q21.3	<i>FLG</i>	Involved in terminal epidermal differentiation and aggregation of keratin intermediate filaments
2q24.3	<i>XIRP2</i>	Involved in actin cytoskeleton and cell–cell junction organization and protection of actin filaments from depolymerization
19p13.2	<i>ACTL9</i>	Involved in cytoskeletal functions
	<i>ADAMTS10</i>	Involved in metalloproteinase activity and assembly of extracellular matrix components
Antigen processing and presentation		
2p13.3	<i>CD207</i>	C-type lectin with mannose binding specificity; major receptor on Langerhans cells; involved in antigen uptake, processing and presentation
6p21.32	<i>HLA-DRB1</i>	Involved in antigen processing and presentation for MHC class II cells
6p21.33	<i>HLA-B</i>	Involved in antigen processing and presentation for MHC class I cells
Regulation of cytokine production		
11p15.4	<i>NLRP10</i>	Involved in regulation of the innate immune system, release of pro-inflammatory cytokines, inhibition of apoptosis and anti-inflammatory response
11q24.3	<i>ETS1</i>	Transcription factor; involved in control of cytokine and chemokine expression
RNA modification		
2p16.1-p15	<i>PUS10</i>	Involved in post-transcriptional modification of structural RNAs and in apoptosis
Unknown		
2p25.1	<i>LINC00299</i>	Long non-coding RNA
Transporter		
3p21.1	<i>RFT1</i>	Oligosaccharide transporter; involved in protein N-glycosylation

Table 1 (cont.) | Susceptibility loci and most plausible candidate gene(s) associated with atopic dermatitis

Susceptibility locus	Most credible candidate gene(s)	Known or proposed function(s)
Extracellular structure organization		
3q13.2	CCDC80	Involved in cell adhesion and matrix assembly
Chromosome organization		
10q21.2	ZNF365	Involved in mitotic cytokinesis and maintenance of genome stability
Regulation of cell motility		
11p13-p12	PRR5L	Involved in regulation of protein kinase C phosphorylation, cell survival, cytoskeletal organization and cell migration
Regulation of cell cycle		
11q13.1	OVOL1	Transcription factor; involved in hair formation and spermatogenesis
Autophagy		
16p13.13	CLEC16A	C-type lectin; involved in regulation of mitophagy, autophagy and mitochondrial health
Vitamin D receptor signalling		
20q13.2	CYP24A1	Involved in vitamin D metabolism

IgE, immunoglobulin E; MHC, major histocompatibility complex; NF- κ B, nuclear factor- κ B; TCR, T cell receptor; TGF β , transforming growth factor- β ; T_H, T helper; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin.

pattern (FIG. 4). Infants often show widely distributed and more-acute skin lesions characterized by severe erythema, oedema, excoriations (scratch marks) and serous exudate manifesting as oozing and crusting; lesions in infants are characteristically located on the face, cheeks and the trunk, with the notable sparing of the diaper (nappy) area (FIG. 4a). In childhood, AD becomes more-localized and chronic with paler erythema, xerosis (dry skin) and more ill-defined skin lesions that commonly affect flexor surfaces (FIG. 4c), and in the most chronic areas the skin is thickened from repetitive scratching. Adolescents and adults can have a diffuse pattern of AD but also localized lesions most typically affecting hands, eyelids and flexures. Adults can have only chronic hand AD or the head-and-neck subtype of AD, which involves the upper trunk, shoulders and scalp (FIG. 4e).

Other features that are commonly observed but are not a prerequisite to establish diagnosis include early onset (typically during the first year of life), a personal and/or family history of atopic diseases, specific IgE reactivity and the presence of generalized skin dryness. Individuals with a predisposition for atopic diseases can also manifest hyperlinearity of the palms and soles, Dennie–Morgan lines (a fold in the skin below the lower eyelid caused by oedema) and Hertoghe sign (thinning or loss of the outermost eyebrows)¹¹⁶. Morphological subtypes of AD include the follicular type, which is characterized by densely aggregated follicular papules (small hard elevation of the skin) and is frequent in dark-skinned individuals and people of Asian origin¹¹⁷, and the prurigo type, which is characterized by erythematous, often excoriated papules and indurated (hardened) nodules and is sometimes seen in patients with long-standing disease.

Severity scoring systems. AD severity can be measured using validated scoring systems such as the Scoring Atopic Dermatitis (SCORAD)¹¹⁸ or Eczema Area and Severity Index (EASI)¹¹⁹. These tools are the preferred

instruments for measuring AD signs¹²⁰; both tools consider erythema, infiltration (swelling), excoriations and lichenification as well as the extent of the area affected to assess clinical signs, and the SCORAD also considers oozing and crusting. The SCORAD is a composite score that attributes ~60% of the total score to intensity of the lesions, 20% to spread and 20% to subjective signs scored by the patient, that is, the severity of clinical signs can only be inferred from the objective SCORAD (oSCORAD; which does not include assessment of symptoms). By contrast, the EASI gives ~50% weight to intensity and 50% weight to extent of lesions. The Patient-Oriented Eczema Measure (POEM) and the Patient-Oriented SCORAD (PO-SCORAD) are the preferred instruments to measure patient-reported symptoms in AD trials¹²¹.

Secondary prevention

Although influencing the genetic background is not yet feasible, secondary prevention strategies based on trigger avoidance (that is, reducing exposure to environmental factors that can trigger AD flares) have been implemented in practical guidelines¹²². Irritants such as air pollutants (for example, traffic exhaust) or indoor pollutants (for example, tobacco smoke and volatile organic compounds, such as propylene glycol and glycol ether) can affect patients with sensitive skin and lead to AD exacerbations^{15,123}. The spectrum of relevant allergens changes with the course of the disease. Food allergens induce flares in a substantial proportion of infants with moderate-to-severe AD, but most food allergies resolve during childhood, with the exception of peanut allergy¹²⁴. By contrast, environmental allergens such as house dust mite, pollen²¹ or animal fur seem to be more-relevant as trigger factors in older children and adults.

The role and temporal relevance of IgE-mediated allergy in AD and consequently the avoidance of putatively relevant allergens are still a matter of debate. The clinical relevance of IgE specific for a suspected

Box 3 | Filaggrin

Filaggrin is a major structural protein in the stratum corneum, the most external layer of the skin. Filaggrin monomers derive from the proprotein profilaggrin, which is abundant in keratohyalin granules in the stratum granulosum. During terminal differentiation of keratinocytes at the transition from the stratum granulosum to the stratum corneum, profilaggrin is rapidly dephosphorylated and cleaved into several functional filaggrin monomers by several endoproteases⁴⁹. In vitro, filaggrin monomers aggregate and align keratin bundles and are assumed to contribute to the mechanical strength and integrity of the stratum corneum⁴⁹. Filaggrin monomers are deiminated and degraded by proteases in the upper layers of the stratum corneum. Filaggrin is a histidine-rich protein; its major metabolites are hygroscopic (absorbing moisture) amino acids and the organic acids *trans*-urocanic acid and pyrrolidone-5-carboxylic acid. Filaggrin breakdown products, together with chloride and sodium ions, lactate and urea, form natural moisturizing factor, a protective coat that has a role in epidermal hydration and barrier function.

allergen can be ascertained by the atopy patch test (a test that is not yet standardized in which fresh whole allergen is applied to the skin under occlusion (covered))¹²⁵ or, more definitively, by exposure tests in a sealed chamber^{21,124}. For suspected food allergy, although there is no standardized testing procedure, the current guidelines propose the administration of the suspected food in a blinded provocation test¹²⁶. For aeroallergens, the skin is exposed under controlled conditions to distinct allergens in an environmental challenge chamber²¹. However, as these tests remain controversial, avoidance recommendations such as encasing mattresses and pillows should be provided only when there is proven evidence of relevant allergen sensitization, and even in such cases, the effects of avoidance strategies might be marginal¹²⁷. Caution is particularly important in regard to eliminating food from diets¹²⁸. A study on peanut allergy has in fact demonstrated that early introduction of peanut allergen in the diet of children with AD who are not already highly sensitized to peanut allergen could prevent the development of sensitization¹²⁹. Similarly, specific allergen immunotherapy is an approach used with the goal of inducing immune tolerance to improve airway atopic disorders. However, a Cochrane review of 12 randomized controlled trials using standardized allergen extracts in children and adults with AD found limited evidence that specific allergen immunotherapy was an effective treatment¹³⁰.

Primary prevention

Successful large-scale primary prevention approaches to hamper the occurrence of AD have not been reported so far. Similarly, systematic reviews failed to show any effect of dietary supplementation¹³¹. A 4-month period of breastfeeding might be advisable for newborn babies at high risk to develop AD, although the effects of breast milk on development of AD and allergy are conflicting¹³². Hypoallergenic milks, such as hydrolysed formula, as well as prebiotics and probiotics have

a moderate protective effect, but overall, the results of the available studies are inconsistent¹³³. Large studies on elimination diets conclude that this approach is not advisable and could even impair oral tolerance. In fact, early exposure to peanut, egg and yogurt could reduce the risk of sensitization^{134–136}. Genetic and inflammation-driven alterations of epidermal barrier function contribute to AD onset, and several pilot trials have indicated that the daily use of emollients from birth in newborn babies who are at high risk of developing AD could be an effective prevention strategy^{137,138}.

Management

The goals of therapy are to reduce pruritus and establish persistent disease control that is sufficient to enable patients to be fully functional at home, work and school. These goals typically require a multistep approach with interventions that are aimed at avoiding relevant triggers, improving the skin barrier, normalizing the skin dysbiosis and reducing inflammation. The best outcomes are achieved when treatment is paired with a formal patient and caregiver treatment education programme^{139,140}.

Therapy selection is largely based on disease severity, with adjustments on the basis of the age of the patient, presence of atopy-related and atopy-unrelated comorbidities, compliance concerns and cost. On the basis of US sales records from early 2017, systemic therapies account for 41% of the \$3.7 billion dollars of total sales, and this percentage will probably increase substantially as the development, licensing and prescription of more costly targeted monoclonal antibodies and small molecule antagonists have an effect on the market¹⁴¹. Recent AD management guidelines from the American Academy of Dermatology¹¹⁶ provide details of the current treatment approaches¹¹⁵. Herein, we describe the available therapies including those commonly used off-label as well as therapies that are in the late stages of clinical development for AD.

Topical therapies

Topical therapies are the mainstay of therapy for patients with mild-to-moderate AD. Moisturizers with non-aqueous emollients (to soften the skin), occlusive agents (to create a physical barrier that contributes to maintaining moisture) and humectants (to attract water) are widely used and produce benefits, such as improved barrier function, reduction in AD signs and symptoms and reduced need for topical corticosteroids (TCSs), when used on a daily basis¹⁴². Emollients reduce the progression to AD when used daily in high-risk infants (who have at least one first-degree relative with any atopic disease) from birth¹³⁷. Several prescription emollient devices with putative barrier enhancing additives like glycyrrhetic acid, ceramide or palmitoylethanolamide have received US FDA approval through the 510(k) medical device clearance process (which is a less rigorous review process than drug approvals) with the notion that they can improve skin barrier functions. However, on the basis of few head-to-head trials, there is no clear consensus on whether these approved topicals are superior to other, less-expensive,

non-prescription compounds, leaving the choice of moisturizer to the health-care provider and patient¹⁴³. These compounds are not approved in the European Union, Australia or Japan.

Topical corticosteroids. TCSs are widely endorsed as the first-line anti-inflammatory treatment and reduce disease recurrence when used intermittently (for example, twice weekly to at-risk skin sites) in patients with established disease. Corticosteroids have pleiotropic effects on the adaptive immune system, reduce *S. aureus* levels and have conflicting effects on measures of skin barrier function^{144,145}. TCSs are grouped into classes (seven in the United States and four in Europe) according to their potency, from very low or lowest potency (highest class number) to very high potency (lowest class number), on the basis of a vasoconstriction assay (the higher the potency, the greater the vasoconstriction); measuring vasoconstriction is considered a high-throughput bioassay indicative of anti-inflammatory potency. The choice of potency is based on disease activity, patient age and anatomical location. Low-potency TCSs are indicated for mild disease, young children and flexural and facial skin lesions. The appropriate intermittent use of TCSs bears little risk¹⁴⁶; however, improper TCS use can cause local adverse effects such as skin thinning, purpura (red spots caused by subcutaneous bleeding), striae (stretch marks), telangiectasias (spider veins), dyspigmentation and acneiform changes (on the face only). Systemic adverse effects from TCSs are very uncommon but can include hypothalamic–pituitary–adrenal suppression and growth retardation¹⁴⁷.

Topical calcineurin inhibitors. Topical calcineurin inhibitors (TCIs) are a unique class of steroid-sparing topical anti-inflammatory agents that were FDA-approved in the early 2000s for use in children of >2 years of age and adults for short-term and chronic intermittent use. The only two FDA-approved TCIs available are tacrolimus (ointment) and pimecrolimus (cream). TCIs inhibit cutaneous T cell activation and proliferation¹⁴⁸. Post-marketing studies have highlighted that TCIs could also have epidermal barrier repair actions^{149,150}. In 2005, the FDA issued a black box warning regarding a potential increased risk of lymphoma associated with TCIs. A meta-analysis of ~4,000 articles identified a modest increased risk of lymphoma in patients with severe AD, but the use of TCIs and TCSs did not seem to significantly contribute to the overall risk³⁴. TCIs are commonly used to treat anatomical areas where the risk of local adverse effects of TCSs is greatest, such as face and flexural skin. However, the use of TCIs is limited by their reduced clinical efficacy (lower than or equal to moderately potent TCSs), burning or pruritus commonly observed during the first week of use (especially with tacrolimus)¹⁵¹, cost and small tube size, which effectively limits the body surface area that can be treated.

cAMP-specific 3',5'-cyclic phosphodiesterase 4 inhibitors. In 2016, the FDA approved a new topical anti-inflammatory class that inhibits the intracellular enzyme cAMP-specific 3',5'-cyclic phosphodiesterase 4

(PDE4). Crisaborole ointment (the first drug in this class and the only one approved so far) is approved for the treatment of patients of ≥2 years of age with mild-to-moderate AD. By inhibiting PDE4, crisaborole promotes the activity of the second messenger cAMP, resulting in a decrease in the production of pro-inflammatory cytokines. The rationale for this therapy came from several studies that had demonstrated that leukocytes from patients with AD have a blunted cAMP response owing to increased PDE4 activity¹⁵². In phase III trials that enrolled patients of ≥2 years of age with mild-to-moderate AD, 32% of patients treated with crisaborole met the primary end point of clear or almost clear skin, a modest increase compared with the 18–25% of patients treated with the vehicle. No serious adverse events were reported, and the main adverse effect was burning or stinging at the site of application¹⁵³. The overall role of crisaborole in AD management has yet to be settled¹⁵⁴, but it could offer another topical nonsteroidal option for use in individuals with mild-to-moderate AD or in anatomically sensitive sites.

Phototherapy

If disease control cannot be achieved with topical measures, short-term phototherapy (usually 4–8 weeks) should be considered. A meta-analysis of randomized controlled trials of phototherapy for the treatment of AD demonstrated that narrow-band ultraviolet B (NB-UVB) light and medium-dose ultraviolet A1 (UVA₁) light are most effective¹⁵⁵. Phototherapy carries several risks including photodamage, local erythema and tenderness, dyspigmentation and, depending on cumulative doses, increased risk of cutaneous malignancies and cataract formation¹⁵⁶. The use of phototherapy is most commonly limited by distance to a treatment centre, time lost from work or home, cost and concomitant treatment with a photosensitizing medication. When topical

Box 4 | Type 2 immunity

The innate and adaptive immune systems can be broadly classified into three main types, which have different functions and involve different immune cells. Type 1 immunity protects against intracellular pathogens, such as viruses; type 2 immunity targets large extracellular parasites, such as worms; and type 3 immunity protects against extracellular microorganisms. Dysregulation of type 1 or type 3 immunity can lead to autoimmune diseases, whereas altered type 2 immune responses are involved in allergic diseases.

Type 2 immunity is a particular arm of the innate and adaptive immune systems that is evolutionarily specialized to protect against extracellular organisms such as helminths and other parasitic agents. However, when these pathways are activated excessively and chronically, they can be damaging rather than protective. Type 2 immune responses initiate at epithelial interfaces, where alarmins such as thymic stromal lymphopoietin, IL-25 and IL-33 activate group 2 innate lymphoid cells, T helper 2 (T_H2) cells and B cells. Effectors of the type 2 immune response include immunoglobulin E as well as effector cells such as eosinophils, basophils and mast cells; IL-4, IL-5, IL-9, IL-13 and IL-31 are secreted by activated T_H2 cells and T_H22 cells, leading to atopic diseases.

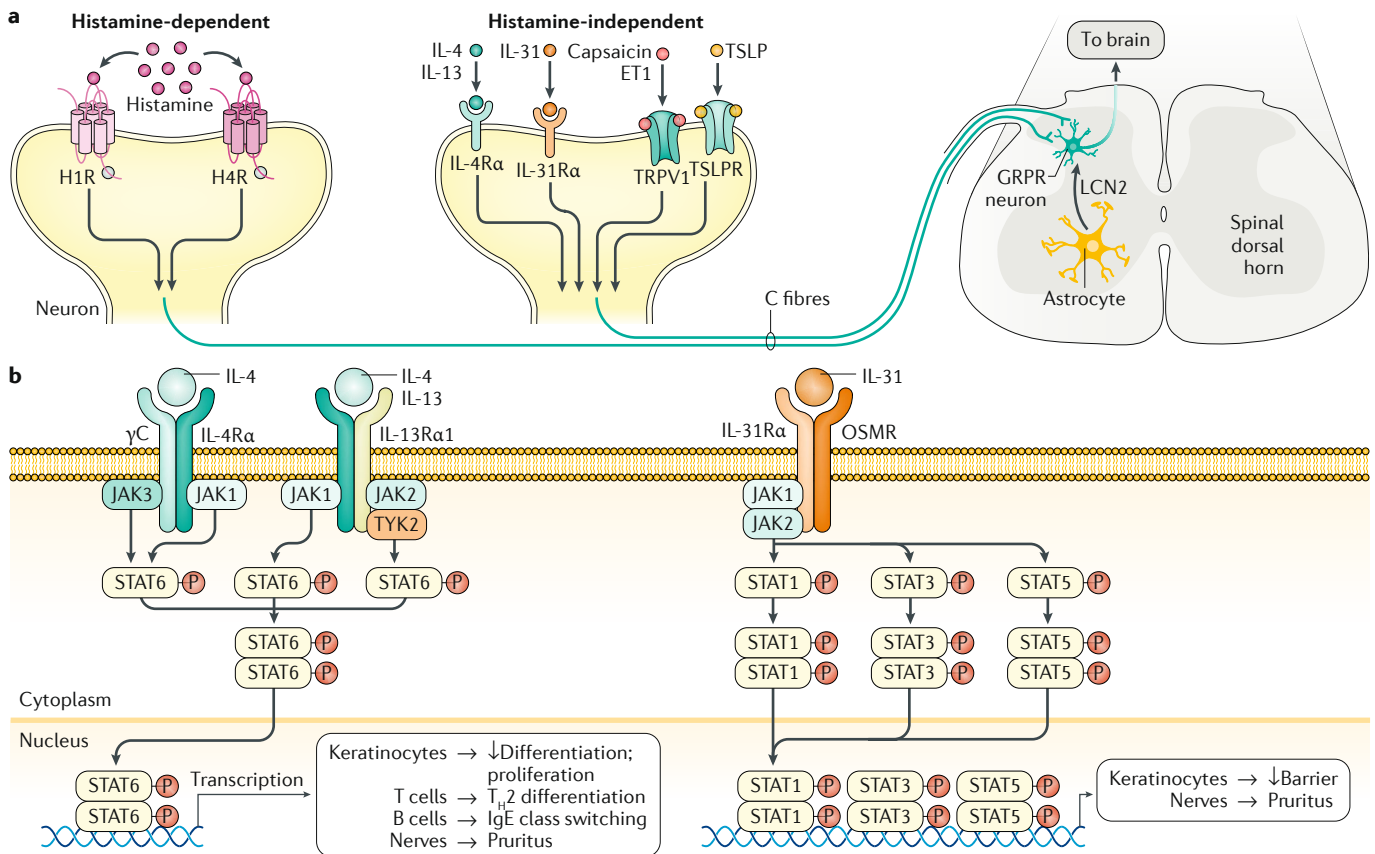


Fig. 3 | Itch pathways and type 2 immunity cytokine signalling in atopic dermatitis. a | Histamine-dependent and histamine-independent itch signalling pathways. Sensory neurons expressing histamine H1 receptor (H1R) and H4R respond to histamine release. In the histamine-independent pathway, type 2 immunity cytokines and thymic stromal lymphopoietin (TSLP) activate neurons expressing transient receptor potential cation channels. C fibres relay the signal to the spinal dorsal horn, where signal transducer and activator of transcription 3 (STAT3)-dependent reactive astrocytes produce lipocalin 2 (LCN2, also known as neutrophil gelatinase-associated lipocalin). LCN2 sensitizes a pruritic processing neuronal network involving neurons expressing gastrin-releasing peptide receptor (GRPR). These events induce a long-term reactive state of astrocytes in the dorsal horn of the spinal segments, which leads to chronic pruritus. **b** | IL-4 and IL-13 are produced mainly by T helper 2 (T_H2) cells, basophils and group 2 innate lymphoid cells. IL-4 binds cytokine receptor common subunit γ C, which activates Janus kinase 3 (JAK3). Both IL-4 and

IL-13 can bind IL-4 receptor subunit- α (IL-4Ra), which activates JAK1. IL-13 can also bind IL-13 receptor subunit- α 1 (IL-13Ra1), which activates non-receptor tyrosine-protein kinase TYK2 and JAK2. The IL-4 and IL-13 receptors are heterodimers formed by IL-4Ra and γ C or IL-4Ra and IL-13Ra1. JAK1, JAK2, JAK3 and TYK2 can all phosphorylate STAT6; phosphorylated STAT6 dimerizes and migrates to the nucleus. STAT6 binds to the promoters of the IL-4-responsive and IL-13-responsive genes and, depending on the cell type, promotes various effects. IL-31 is produced mainly by T_H2 cells. IL-31 binds to IL-31 receptor subunit- α (IL-31Ra) and activates JAK1 and/or JAK2, which in turn phosphorylate STAT1, STAT3 and STAT5. Dimers of these signal transducers translocate to the nucleus and activate IL-31-responsive genes. ET1, endothelin 1; IgE, immunoglobulin E; OSMR, oncostatin-M-specific receptor subunit- β ; TRPV1, transient receptor potential cation channel subfamily V member 1; TSLPR, TSLP protein receptor (also known as cytokine receptor-like factor 2 (CRLF2)). Adapted with permission from REF.²²⁸, Elsevier.

therapies and phototherapy fail or become unacceptable or impractical, systemic therapy is indicated¹⁵⁷.

Systemic immunosuppressants

Systemic non-biologic therapies commonly used include the nonspecific immunosuppressants ciclosporin, azathioprine, methotrexate and mycophenolate mofetil. In a systematic review of 34 randomized controlled and uncontrolled trials testing the efficacy of ciclosporin in adults and children, patients treated with ciclosporin achieved a mean disease improvement of 55% from baseline measures after 6–8 weeks of treatment¹⁵⁸. Before the advent of biologics, ciclosporin was the most effective treatment for severe, refractory AD, and, therefore, it has been licensed for short-term treatment in many European countries and in Japan. The use of ciclosporin

is limited by potential toxicities, in particular nephrotoxicity¹⁵⁹; thus, most guidelines do not recommend continuous therapy for >1–2 years^{122,160}.

Both azathioprine and methotrexate are effective and safe off-label treatments for severe AD, even in children^{161–163}. In a non-inferiority trial, 92% of patients treated with methotrexate and 87% of patients treated with ciclosporin achieved an EASI50 (reduction of baseline EASI by 50%) response at week 20 (REF.¹⁶⁴). In another small randomized comparison trial, both methotrexate and azathioprine led to a 40–50% reduction in clinical scores by week 12 (REF.¹⁶⁵). Of those patients who were available for >2 years of follow-up, 20% discontinued therapy because of disease control, 20% discontinued therapy owing to lack of efficacy, and 9% discontinued therapy owing to adverse events. All the patients

Box 5 | Differential diagnoses of atopic dermatitis

For each age group, the differential diagnoses are listed in order of probability (from highest to lowest).

Infants and toddlers (0–24 months of age)

Seborrheic dermatitis, ichthyosis vulgaris, scabies, psoriasis, pyoderma, phenylketonuria, anhidrosis hypotrichotica, coeliac disease, dedicator of cytokinesis protein 8 (DOCK8) deficiency syndrome, Di George syndrome (also known as 22q11.2 deletion syndrome), agammaglobulinaemia, immunoglobulin A deficiency and Netherton syndrome

Children and adolescents (2–16 years of age)

Tinea manuum and/or tinea pedum, impetigo, psoriasis and pityriasis rosea

Adults (>16 years of age)

Allergic contact eczema, psoriasis, pityriasis rosea, cutaneous T cell lymphoma, pityriasis rubra pilaris and asteatotic eczema

who remained on treatment had an EASI50 response at year 2, and 100% and 94% of the patients taking methotrexate and azathioprine had an EASI75 response, respectively¹⁶⁶. Mycophenolate mofetil, another drug used off-label for AD treatment, has a more-favourable safety profile, but because of its more-limited efficacy, it is considered a third-line option or one best used as a maintenance therapy after achieving disease control with another more-effective systemic treatment¹⁶⁷.

Drug survival studies, aimed at identifying factors that associate with the length of time a patient continues a drug therapy, have demonstrated by univariate Cox regression that older age and male sex were associated with decreased drug survival and that this association was linked to a higher rate of disease control and of adverse effects with age, in particular in patients of ≥ 45 years of age¹⁶⁸. A study comparing azathioprine and mycophenolate mofetil found that they had very similar drug survival profiles, but azathioprine was discontinued mainly because of adverse effects, whereas mycophenolate mofetil was discontinued mainly owing to ineffectiveness¹⁶⁹.

Of note, although systemic corticosteroids are FDA-approved for the treatment of AD, published treatment guidelines suggest that they should be used only as a last resort to manage acute flares or as a bridge to the use of another systemic, steroid-sparing therapy¹⁷⁰. Systemic corticosteroids are not advised for long-term management of AD.

Systemic immunomodulating biologics. Dupilumab is the first biologic that has been approved by the FDA and the [European Medicines Agency](#) (EMA) for the treatment of adults with moderate-to-severe AD. It is a fully human monoclonal antibody against IL-4Ra that blocks both IL-4 and IL-13 signalling. Trials are underway to assess its safety and effectiveness in paediatric AD as well as for the treatment of adults with asthma, nasal polyposis or chronic sinusitis, eosinophilic oesophagitis and alopecia areata. Dupilumab treatment of adults with AD demonstrated significant improvements in disease severity as measured by the EASI and Investigator's Global Assessment (IGA)^{104,171,172}.

In phase IIb trials, 62% of patients treated with dupilumab achieved an EASI75 response compared with only 15% in the placebo group after 16 weeks¹⁰⁴. These early phase data have been supported by two large phase III, randomized controlled trials¹⁷¹. When dupilumab was combined with TCSs, the proportion of patients achieving an EASI75 response increased even further to ~65% compared with 22% of patients who received TCSs only¹⁷². The most frequent adverse effects are ocular complaints (dry eye, conjunctivitis and blepharitis (inflammation of the margins of the eyelids)) and nasopharyngitis, which are reported by up to 20% of patients, and injection-site reactions in up to 10% of patients¹⁷².

Complications

In individuals with AD, epidermal barrier dysfunction¹⁷³, defects in innate immune responses¹⁷⁴ and underlying type 2 immunity and inflammation can facilitate the growth of commensal or opportunistic microorganisms, including *S. aureus*¹⁷⁵. *S. aureus* can play a role in allergen sensitization and possibly mediates disease flares, and *S. aureus* colonization can also develop into infections (impetiginization) of pre-existing skin lesions, which clinically present as honey-coloured blisters and crusts¹⁷⁶. Impetiginization is usually treated with topical antiseptics or antibiotics, but systemic antibiotics might be needed in severe cases.

In patients with AD, antiviral cutaneous defences seem to be defective as well, as patients sometimes develop severe viral complications, such as eczema herpeticum (EH), which is a widespread skin infection with herpes simplex virus that occurs in up to 3% of patients with AD and is virtually never seen in healthy individuals¹⁷⁷. EH is typically accompanied by systemic signs, including fever, headache, lymph node swelling and increased mononuclear cells in the peripheral blood; EH can even lead to meningitis or hepatitis and be life-threatening if misdiagnosed and/or left untreated. Thus, EH is considered a dermatological emergency. Interestingly, patients with the atopic dermo-respiratory syndrome (AD with concomitant allergic asthma and rhinitis) have the highest risk of developing this viral complication¹⁷⁸.

AD is also associated with molluscum contagiosum, which is a viral skin infection affecting up to 11.5% of children with AD, although the strength of this association is less clear than in EH¹⁷⁹. Infection with molluscum contagiosum virus causes small dome-shaped, skin-coloured, pearly nodules with a central depression that are most commonly observed on the trunk, flexures and in the genital area¹⁸⁰. The lesions can become disseminated, resulting in up to several hundred lesions, and this AD variant is called eczema molluscatum. Coxsackie virus superinfection has also been reported to lead to eczema coxsackium, a disseminated skin infection in patients with AD¹⁸¹.

Treatments in clinical trials

AD drug development has been thriving, with many biologics and small molecule antagonists in phase II and phase III trials targeting different signalling pathways, including type 2 immunity, JAK and itch pathways, among others (TABLE 2). Several agents in development aim at improving the intractable itch associated with

AD, and some of these agents could also have some anti-inflammatory or epithelial barrier repair actions.

JAK inhibitors can block a range of cytokine, growth factor and/or hormone receptor signalling pathways depending on their relative specificity; many JAK inhibitors are in development as oral therapies for moderate-to-severe AD or as topical treatments for mild-to-moderate AD (TABLE 2). The challenge will be to identify the JAK specificity that provides the ideal risk–benefit balance for patients with AD.

Monoclonal antibodies, such as mepolizumab, benralizumab and reslizumab, have been developed to neutralize IL-5, which promotes eosinophil recruitment, and all three are now FDA-approved to treat asthma. Thus far, only mepolizumab has been evaluated in AD. The first study was a small, single-dose, 4-week study and showed no effect¹⁸², and another small, proof of concept, 16-week study was terminated because of futility. These results question

the benefit of this anti-eosinophil strategy in adults with AD. Lastly, two small studies with ustekinumab, which targets the common p40 subunit of IL-12 and IL-23 and is an FDA-approved therapy for psoriasis, failed to show efficacy in adults with moderate-to-severe AD^{183,184}.

Quality of life

The effect of dermatological diseases and particularly of AD on the quality of life (QoL) of both the patient and their families and caregivers has received considerable attention since the early 2000s. The mean Dermatology Life Quality Index (DLQI) scores from patients with AD were similar to those of patients with psoriasis or urticaria (hives) but much greater than those of patients with alopecia, rosacea (facial redness and pustulations) or cutaneous lupus erythematosus¹⁸⁵. In the 2013 Global Burden of Disease Study, dermatitis (atopic, contact and seborrheic) was the skin condition with the greatest effect on disability-adjusted life years (DALY)¹⁸⁶, a measure of disease burden that takes into account both the quality and the quantity of years lived. Although the HOME initiative³ has identified QoL as a core outcome to be measured in AD treatment trials, no well-validated instrument has been identified¹⁸⁷ that can quantify the physical, social, emotional, cognitive, work-related and disease-related symptoms, as well as the economic effects of AD, and perform well in both sexes and across all ages (infants, children and adults) and ethnic groups. The QoL instruments most commonly used in AD clinical trials are the DLQI and the Infants' Dermatology Quality of Life Index (IDQOL)¹⁸⁸. Of note, QoL measures do not consistently reflect investigator-assessed objective measures like EASI and oSCORAD. This observation highlights the importance of a QoL tool that can take into account the different disease domains, in particular signs and symptoms (for example, itch and burning), sleep quality, work performance and social and emotional well-being, to quantify the different aspects of the individual burden of AD in a real-world setting.

On the basis of QoL measures, AD ranks second to cerebral palsy among chronic childhood disorders¹⁸⁹. QoL studies in children and young adults with AD have found that itch has an adverse effect on sleep, treatment preferences, participation in sports and extracurricular activities, clothing choices and social interactions¹⁹⁰. Studies in adults confirm the effect of itch on QoL metrics¹⁹¹. One-third of adults with AD reported that their disease even affected their clothing choices as well as shaving or makeup habits¹⁹². The location of AD lesions, in particular if they are on the facial or genital areas, substantially affects QoL measures¹⁹³. Adults with AD report 6% higher rates of work absenteeism than an age-matched and sex-matched control population¹⁹⁴, and children with AD experience more school absences than their unaffected peers¹⁹⁵. In a cross-sectional study, adults with AD with one of the common *FLG* mutations had reduced health-related QoL (measured with DLQI) compared with adults with AD who did not have these mutations¹⁹⁶.

QoL metrics are increasingly used in interventional AD trials. In phase III dupilumab trials, significant

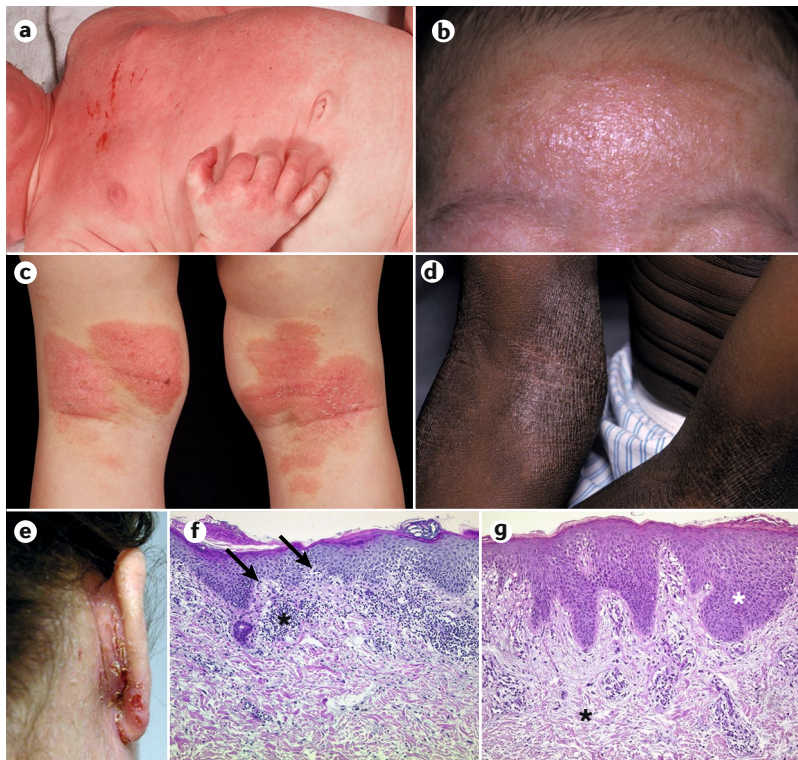


Fig. 4 | Clinical manifestations of atopic dermatitis. **a** | Extensive erythema on the trunk of a 6-month old baby, with excoriations. Lesions are characteristically located on the face, cheeks and trunk, with the notable sparing of the diaper area. **b** | Acute vesicular atopic dermatitis (AD) of the face of a 2-year-old Asian child. **c** | In childhood, AD becomes more-localized and chronic and commonly affects flexor surfaces. **d** | In the most chronic areas, the skin is lichenified (thickened) from repetitive scratching; lichenification is often more-marked in patients of African descent. **e** | Adults may have only chronic hand AD or the head–neck–dermatitis type, which involves the upper trunk, shoulders and scalp. **f,g** | On histopathology, AD cannot be reliably distinguished from other forms of eczematous dermatitis. The acute exudative lesion is characterized by epidermal acanthosis (increased thickness) and spongiosis (arrows), dermal oedema and a perivascular and/or periappendageal lymphocytic and eosinophilic infiltrate (asterisk), as visualized by haematoxylin and eosin staining (part **f**). The chronic lichenified skin lesion has acanthosis (white asterisk), hyperkeratosis, parakeratosis, a dense dermal infiltrate of mononuclear cells and increased mast cells together with fibrosis (black asterisk), as visualized by haematoxylin and eosin staining (part **g**). Parts **b** and **d** appear with permission from VisualDx.

Table 2 | Pharmacological therapies in development for the treatment of atopic dermatitis

Target	Drug	Biologic or SMA	Symptom severity indication	Notes	Refs
Systemic					
Anti-T_H2 cell signalling					
IL-13	Tralokinumab	Biologic	Moderate to severe	- Humanized monoclonal antibody - Phase II trials completed - Modest effect on EASI and IGA measures compared with the placebo group after 16 weeks - Possible confounding effect of concomitant use of TCSs in both arms	229
	Lebrikizumab	Biologic	Moderate to severe	- Humanized monoclonal antibody - Phase II trials completed - Modest benefit in EASI50 compared with placebo after 12 weeks - Possible confounding effect of concomitant use of TCSs in both arms	230
TSLP	Tezepelumab	Biologic	Moderate to severe	Phase IIa study failed to meet primary end point of improvement in EASI after 12 weeks	231
IL-33	ANB020	Biologic	Moderate to severe	- Monoclonal antibody - In phase IIa trial, 75% of patients ($n=9$) achieved an EASI50 by day 15, with efficacy sustained for >4 months - Well-tolerated; headache most common adverse event	232
OX40	GBR830	Biologic	Moderate to severe	- Monoclonal antibody - Greater proportion of patients achieving EASI50 and EASI75 than the control arm at day 71 - Headache most common adverse event	233
CRTH2	Fevipirant	SMA	Moderate to severe	- Phase II trials completed - Minimal benefit	107
	Timapirant	Biologic	Moderate to severe	- Phase II trials completed - Minimal benefit	107
Anti-T_H22 cell signalling					
IL-22	Fezakinumab	Biologic	Moderate to severe	- Monoclonal antibody - Significant reductions in body surface area affected but not in SCORAD after 12 weeks	234
Anti-pruritic					
IL-31 α	Nemolizumab	Biologic	Moderate to severe	- Monoclonal antibody - In a phase II trial, significant reductions in itch (VAS), but not in EASI or body surface area affected, compared with placebo after 12 weeks - Discontinuation owing to exacerbation of atopic dermatitis, peripheral oedema and elevated creatine kinase levels more common in the treatment arm than in the placebo arm	107
IL-31	BMS-981164	Biologic	Moderate to severe	Dose-escalation phase I study completed; results not yet available	NA
NK1R	Tradipitant	SMA	Moderate to severe	- Phase II study completed - Significant reductions in itch (VAS) and SCORAD after 8 weeks - Well-tolerated	235
Anti-inflammatory					
JAK1 and JAK2	Baricitinib	SMA	Moderate to severe	- Phase II study completed - EASI50 achieved by 61% of patients treated with baricitinib + TCSs compared with 37% of patients in the control arm (TCSs alone) ($P=0.027$) - Significant improvement in SCORAD - Possible confounding effect of concomitant use of TCSs in both arms - Most common adverse events were headache, increased creatine kinase levels and nasopharyngitis	236
JAK1	Upadacitinib	SMA	Moderate to severe	- Phase II study completed - Clinical and patient-reported outcomes 74% reduction in EASI score compared with 23% in the placebo arm - IGA0 or IGA1 achieved by 50% of patients treated with upadacitinib compared with 2% of patients in the placebo arm - Detailed results not yet available	237
	PF-04965842	SMA	Moderate to severe	- Phase IIa study completed 82% reduction in EASI score compared with 35% in the placebo arm - IGA0 or IGA1 achieved by 44.5% of patients treated with PF-04965842 compared with 6.3% of patients in the placebo arm ($P<0.003$) - Detailed results not yet available	238
JAK and SYK	ASN002	SMA	Moderate to severe	- Phase IIa study completed - EASI75 achieved by 63% of patients treated with ASN002 - Detailed results not yet available	239

Table 2 (cont.) | Pharmacological therapies in development for the treatment of atopic dermatitis

Target	Drug	Biologic or SMA	Symptom severity indication	Notes	Refs
Systemic (cont.)					
Anti-inflammatory (cont.)					
H4R	ZPL389	SMA	Moderate to severe	- Phase IIa study completed 50% reduction in EASI score compared with 27% in the placebo arm - Detailed results not yet available	240
Topical					
Anti-inflammatory					
JAK1 and JAK3	Tofacitinib	SMA	Mild to moderate	82% reduction in EASI score compared with 30% in the vehicle arm at week 4 in a phase IIa, randomized, double-blind, vehicle-controlled study (NCT02001181)	241
JAK1, JAK2 and JAK3	JTE-052 (delgocitinib)	SMA	Mild to moderate	42–73% reduction in modified EASI score compared with 12% in the vehicle arm in a phase III randomized, double-blind, vehicle-controlled study	242
JAK1 and JAK2	Ruxolitinib (INCB018424)	SMA	Moderate to severe	Phase II, randomized, dose-ranging, vehicle-controlled and triamcinolone 0.1% cream-controlled study to evaluate the safety and efficacy in progress (NCT03011892)	NA
PDE4	Roflumilast	SMA	Moderate	Phase IIa, 15-day, randomized, parallel group, double-blind, multi-centre, vehicle-controlled trial concluded (NCT01856764)	NA
	RVT-501	SMA	Mild to moderate	Phase II randomized, vehicle-controlled, double-blind study in paediatric patients in progress (NCT03394677)	NA
AhR	Tapinarof	SMA	Moderate to severe	Phase I, open-label, two-cohort sequential study in adults to assess systemic pharmacokinetics, safety and preliminary efficacy (NCT02564055)	243

The main data sources for this table were [ClinicalTrials.gov](https://www.clinicaltrials.gov/), the [US FDA](https://www.fda.gov/) and the [European Medicines Agency](https://www.ema.europa.eu/); for the latest updates, visit these websites. Note that not all compounds currently under development are listed in this table. AhR, aryl hydrocarbon receptor; CRTH2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; EASI, Eczema Area and Severity Index; EASI50, 50% reduction in the EASI score; EASI75, 75% reduction in the EASI score; H4R, histamine H4 receptor; IGA, Investigator's Global Assessment; IGA0, clear; IGA1, almost clear; IL-31Ra, IL-31 receptor-α; JAK, Janus kinase; NA, not available; NK1R, NK-1 receptor (also known as substance P receptor); OX40, OX40L receptor; PDE4, cAMP-specific 3',5'-cyclic phosphodiesterase 4; SCORAD, Scoring Atopic Dermatitis; SMA, small molecule antagonist; SYK, tyrosine-protein kinase SYK; TCSs, topical corticosteroids; T_H, T helper; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale.

improvements were seen in both skin-specific and general health-related QoL measures in the dupilumab arm compared with the placebo arm, and these improvements were clinically meaningful¹⁹⁷. Patient-reported QoL metrics will assist health-care providers in determining which treatments are the best option for an individual and will be used by insurers to perform cost-benefit analyses to make economic decisions about access to expensive drugs.

Outlook

Our understanding of AD has made major advances, with insights gained into the epidemiology, burden of disease and comorbidities. In particular, we now better understand AD pathogenesis and the complex interplay between epidermal barrier dysfunction and immune activation. These insights have contributed to the development of effective biologics specifically targeting dysregulated immune pathways and are a driving force leading to prevention studies based on 'barrier therapy' (that is, prevention of barrier damage) to minimize transcutaneous allergic sensitization. These barrier interventions are low-cost, population-level interventions that could be applied widely across both the developed and the developing world. Of note, it remains to be determined whether primary prevention or early treatment can halt progression to food and respiratory allergies, as well as other non-atopic AD comorbidities. Findings from molecular research and trials on targeted therapeutics demonstrate that AD is a heterogeneous disease^{173,198} that probably comprises many different endotypes with

distinct pathological features and clinical implications. The identification and characterization of disease subtypes will be key to understand disease trajectories and help to develop targeted prevention and management approaches; there are now increasing research efforts to identify and characterize AD endotypes and to develop diagnostic biomarkers, for example, using data from genomics, transcriptomics¹⁹⁹ and proteomics²⁰⁰. Individuals with AD will benefit from a precision medicine approach, for which the discovery and validation of relevant biomarkers will be crucial for the stratification of the disease in more-homogenous subgroups that probably respond similarly to prevention and therapeutic strategies.

The changing prevalence patterns in both developed and developing countries offer opportunities for epidemiological investigations that could yield relevant insights into disease aetiology. High-throughput genetic studies, including whole genome sequencing, will provide insights into disease pathogenesis and could direct therapeutic development. With international initiatives to better define and harmonize core outcomes for AD trials, searchable medical records³, well-characterized registries of patient with AD^{166,201} and high-throughput molecular technologies coupled with statistical and computational tools²⁰², there is legitimate hope that the application of precision medicine principles will soon be a reality for patients with AD.

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Author contributions

Introduction (A.D.I. and S.W.); Epidemiology (S.W.); Mechanisms/pathophysiology (all authors); Diagnosis, screening and prevention (T.B.); Management (L.A.B., T.B., A.D.I. and S.W.); Quality of life (L.A.B.); Outlook (A.D.I. and S.W.); Overview of Primer (A.D.I. and S.W.).

Competing interests

S.W. has received honoraria for invited lectures from and served on advisory boards for Galderma, Novartis, Pfizer, Regeneron and Sanofi and has received research funding from La Roche-Posay, Novartis, Pfizer and Sanofi. L.A.B. has received consulting fees from AbbVie, AnaptysBio, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Lilly, Novan, Novartis, Realm Therapeutics, Regeneron and Sanofi-Genzyme; she is principal investigator for clinical trials for AbbVie, Realm Therapeutics and Regeneron and is a stock owner of Medtronic and Pfizer. T.B. has received honoraria for invited lectures from and served on consultant and/or advisory boards for AbbVie, Allmiral, AnaptysBio, Asana Biosciences, Celgene, Daiichi-Sankyo, Dermavant, Galapagos, Galderma, Glenmark, GlaxoSmithKline, Kymab, LEO Pharma, La Roche-Posay, Lilly, L'Oréal, Menlo, Novartis, Pfizer, Roche-Genentech and Sanofi-Genzyme; he was principal investigator for clinical trials with Galderma, LEO Pharma, Lilly, Menlo, Pfizer, Regeneron–Sanofi and Roche–Genentech. K.K. has received honoraria for invited lectures from and served on consultant and/or advisory boards for Chugai, Kyowa Hakkō Kirin, LEO Pharma, Mitsubishi Tanabe, Maruho, Pola and Regeneron–Sanofi; he was principal investigator for clinical trials with Japan Tobacco, Maruho and Regeneron–Sanofi. A.D.I. has received honoraria for invited lectures from and served on consultant and/or advisory boards for AbbVie, Galderma, Lilly, Novartis, Pfizer, Roche–Genentech and Sanofi-Genzyme; he was principal investigator for clinical trials with AbbVie and Regeneron–Sanofi.

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