Chapter

Atopic Dermatitis in Adults: Epidemiology, Risk Factors, Pathogenesis, Clinical Features, and Management

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Abstract

Atopic dermatitis (AD) is an itchy chronic relapsing inflammatory skin condition mostly affecting children than adults. Eczematous conditions are common worldwide with increase in the prevalence in both developed and developing countries. AD in adults is of two types – the first type starts as AD in childhood and gradually progresses to adulthood (Persistent AD) and the second type results from AD developing in adulthood (Adult-onset AD). The article reviews and discusses this condition in adults considering the epidemiology, risk factors, pathogenesis, diagnostic criteria, and management of this condition.

Keywords: Atopic dermatitis, Adult, Adult-onset Atopic dermatitis, Eczema

1. Introduction

Atopic dermatitis (AD) is an itchy chronic relapsing inflammatory skin condition mostly affecting children than adults with atopy. Atopy was derived from the Greek word "atopos" by Coca and Cooke in 1923 for the grouping of asthma, hay fever and asthma. [1] In an article by Kanwar, atopic dermatitis (AD) or atopic eczema was defined as "an itchy, inflammatory skin condition characterized by poorly defined erythema with edema, vesicles, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage," [2] and in the year 2000, Bannister and Freeman originated the term adult-onset atopic dermatitis for the condition in adulthood. [3] AD usually occur as a continuum of childhood AD but few cases start in adulthood, hence, the term - Adult onset AD. AD in adults is of two types – the first type occurs as AD in childhood and progresses to adulthood condition (Persistent AD) while the second type results from AD developing in adulthood (Adult-onset AD). Eczema in adults usually runs a prolong course impairing quality of life, relationships and sex life, and occupation. [4]

Atopy refers to "the genetic tendency to develop allergic diseases such as allergic rhinitis, asthma and atopic dermatitis (eczema). Atopy is typically associated with heightened immune responses to common allergens, especially inhaled allergens

and food allergens." [5] Rang et al. defined atopy as 'a familial hypersensitivity of the skin and the mucosa to environmental substances, associated with increased production of immunoglobulin E (IgE) or altered pharmacologic reactivity.' [6] The ETFAD/EADV Eczema task force consensus 2020 defines atopy as the 'familial tendency to develop Th2 responses against common environmental antigens. [7]

The definition by ETFAD/EADV encompasses both subtypes of atopy – the extrinsic (IgE-associated) subtype, and the intrinsic (non-IgE-associated) subtype. Most AD affected persons have atopic diathesis. The Japanese Dermatological Association defines atopic diathesis as: (1) Personal or family history (asthma, allergic rhinitis and/or conjunctivitis, and atopic dermatitis), and/or (2) Predisposition to overproduction of immunoglobulin E (IgE) antibodies. [8] The Japanese Dermatological Association criteria is based on three clinical features that must be present for diagnosis of AD: (1) pruritus, (2) exanthematous features and their distribution, and (3) chronically relapsing course.

2. Etiology

The increasing number of adult AD cases in recent years has elicited interest in determining factors causing and modifying the disease in adults. Susceptibility to AD is attributable to both genetic and environmental causes. [9] The study by Thomsen et al., showed that AD susceptibility and incidence are mainly due to genetics with 82% cases of AD associated with genes and 18% associated with nonshared environmental factors. [9] A monozyotic twin of an affected person has a sevenfold risk of developing AD compared with a threefold increased risk in dizygotic twin. [9]

Intrinsic IgE-mediated allergic inflammation may play an important role in the pathobiology of elderly AD, similar to other age groups of AD. [10] About 5–15% of cases have intrinsic non-IgE-allergic eczema. [4] Most of the adult AD patients have sensitivity to aeroallergens such as cat epithet, dog epithel and housedusthouse dust mites [11] while common food allergies affect only few. [4] There is a high incidence of contact sensitization to environmental allergens such as nickel (in metals), thiomersal (in eyedrops), fragrance mix (in cosmetics) and lanalcolum (in cosmetics) in adult AD. [11] An increased occurrence of occupational allergic and irritant contact dermatitis among adult AD cases have also been observed. [4] Immunoglobulin E-mediated tests, atopy patch tests (APT), epicutaneous tests (ET), in vitro allergy and Prick tests are usually positive on contact with environmental allergens and to aero allergens. [11]. Pollens are associated with seasonal relapse of AD.

There is specific immediate and delayed sensibilization to Malassezia sympodialis in both intrinsic and extrinsic AD in adults. High rates of sensitization to Dermatophagoides farinae and/or Dermatophagoides pteronyssinus have been documented in patients with extrinsic allergy. House door mite (HDM) refers to a large number of dust dwelling mites including the American HDM, Dermatophagoides farinae Hughes, and the European HDM, Dermatophagoides pteronyssinus. HDM is a common household aeroallergen known to cause asthma, allergic rhinitis and AD. The indoor level of HDM is associated with the severity of skin lesions. [12]

The proportion of contact sensitization to environmental allergens in the 34 adult atopic patients was remarkable (14 of 34, 41%). Out of the verified contact allergens, nickel, fragrance mix, thimerosal and lanalcolum proved to be relevant. House dust mite and cat epithel proved to be the most common relevant aeroallergens. *D. pteronyssinus* and D. farinae sensibilization was high, particularly

in patients with severe skin symptoms on the face, eyelids and hands. Pollens should be considered in patients with seasonal relapse of AD. Sensitization to animal epithel was usually indicated by the flare-up of skin symptoms upon contact with animals. The relevance of the eliciting effects of sensitization could easily be supported in most cases by the medical history and the distribution of skin symptoms. In some adult AD patients with long-lasting AD, the relevance of triggering factors is hard to determine.

The intrinsic (non-IgE-allergic) eczema subtype affects 5–15% of cases. Classical food allergy has a low importance, although non-IgE-mediated and pseudoallergic reactions can cause eczema. Sensitivity to aeroallergens, especially dust mite, is demonstrated in the majority of adult AD patients, including elderly adults, by immunoglobulin E-mediated tests and/or atopy patch tests. Occupational allergic and irritant contact dermatitis is increased. In adults, as in children, *Staphylococcus aureus* colonization is very high, whereas adult skin is more heavily colonized with Malassezia yeasts. Immediate and delayed sensitization to Malassezia sympodialis is specific for intrinsic and extrinsic AD, occurring especially in head-and-neck eczema. [4]

In the study by Pónyai et al., [11] atopy patch and epicutaneous tests (APT, ET), which were supplemented by in vitro allergy and Prick tests – sensibilization was evaluated by the comparison of in vivo and in vitro test results, medical history and skin symptoms. The incidence of contact sensitization to environmental allergens was remarkable: 13 of the EG, 1 of the IG (14 of 34, 41%) The allergens causing positivity were nickel (6 of 13), thiomersal (3 of 13), mercury-amidochlorate (3 of 13), mercury-chloride (2 of 13), iodine chlorhyrdoxyquin (1 of 13), lanalcolum (1 of 13) and fragrance mix (1 of 13). Among the detected allergens, the following were relevant: lanalcolum (1 of 13: cosmetics), fragrance mix (1 of 13: cosmetics), nickel (1 of 13: metal objects), thiomersal (1 of 13: eyedrops).

3. Epidemiology

Atopic dermatitis often develops in infancy with *about* 75% occurring at less than 6 months and 90% before 5 years with about 60–70% resolving in the early teenage years. [1] AD is manly a disease of children with prevalence of 10–20% in children in developed countries. [13] A prevalent rate of 6% was found among children by Oninla et al. [14] at a dermatology centre while Ayanlowo et al. [15] documented a prevalence of 15% at another dermatology centre in Nigeria, a developing country.

Adult AD prevalence is 1–3% of adults world-wide. [4] Approximately 40% of childhood AD persist till adulthood. [16] Adult-onset AD was reported by 1 out of 4 adults with AD. [17] Variable age of onset of adult AD from 18 to 71 years has been reported. [2] About 9% of the cases seen at a contact dermatitis clinic had AD with first onset at 20 years and above while an additional 8% had both adult-onset AD and contact dermatitis. [18] An incidence rate of 18% was reported among adults presenting at a contact dermatitis clinic in a study by the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh. A female preponderance was found in adult AD in some studies though no gender predilection was reported in children. [16, 18]

4. Risk factors

Atopic dermatitis runs a chronic course with acute exacerbations due to triggers such as exposure to allergens (commonly pollens), skin irritants (for example

woolen fabrics, exfoliating soaps, and detergents), stress conditions, skin dryness, dry weather conditions, skin infections and food such as peanuts, gluten, eggs, soy, dairy products and alcohol. [17] Persistence of atopic dermatitis till adulthood was associated with early onset AD, childhood allergic rhinitis, hand eczema, allergic contact dermatitis and increased specific IgE to *Malassezia furfur*. [19]

5. Pathogenesis

Various studies reported AD as a disease resulting from a complex interplay of genetic factors, immunologic mechanisms, biochemical factors, environmental triggers, and pharmacologic factors. [20–24] Sehra et al., [24] described the pathogenesis of this disease and stated that it should translate to treatment strategies. In the review by Leung, [20] AD was initially considered as a disease mediated by a bone-marrow derived cell. This was based on the report that a bone marrow transplant from an AD donor in positive immediate skin tests and symptoms of atopy in the recipient. Also, patients with primary T cell immunodeficiency disorders were found to have elevated serum IgE levels, eosinophilia, and skin lesions of AD. Recently, Leung along with other researchers' reported that AD occurs as a complex interplay of immunologic, microbial, and epithelial interactions. [25]

Recent evidence also revealed that the underlying pathogenesis of AD has shifted from focusing primarily on generalized immune system abnormalities in Th1/Th2 cells to a complex interplay between primary epithelial barrier defect in skin membrane (possibly a genetic defect) and dysregulation of immunological mechanisms involving specific signaling pathways. [25, 26] These abnormalities lead to membrane barrier defects resulting in increased transepidermal water loss (TEWL) and increased allergen exposure as well as immunologic alteration toward atopy. [27]

The exact pathogenesis remains unclear and the underlying mechanism that is well known in the disease development and progression has been atopy. Children with early onset AD often develop allergies to common environmental or food allergens or infective agent [28] with positive skin prick test (SPT) or elevated antigen-specific serum immunoglobulin E (IgE). This type of AD where specific IgE plays a central role in AD is known as Extrinsic AD. The severity of AD has been found to correlate directly with the number of SPT and/or levels of antigen-specific IgE. [29] Extrinsic form accounts for about 45–75% of AD cases. [24]

Although total Ig E elevation is mostly seen in many AD individuals, other factors also modulate the pathophysiology of AD giving rise to the non-atopic or non-T-2 inflammation form of the disease. These are: genetic factors, age, gender, maternal history of atopy, [24] ethnicity, [30] socioeconomic status, [31] environmental factors, and early daycare attendance. [24] The intrinsic form might also affect as many as two thirds of AD individuals. [32]

5.1 Pathogenic mechanisms

5.1.1 Epidermal barrier dysfunction

A strong family history has been reported in 40–60% of AD patients with filaggrin (FLG) null mutation in 20–30%. [33, 34] Genetic mutations involving the epidermal differentiation complex (EDC) gene on chromosome 1q21 impairs epidermal differentiation resulting in stratum corneum barrier dysfunction. [35] The nonsense mutations occur in the EDC gene encoding FLG which is also implicated in asthma associated with AD. [36–38] The gene codes for profilaggrin, a large

precursor protein molecule which is subsequently hydrolyzed to ten to twelve units of FLG. [39]

Palmer et al., reported two independent loss-of-function genetic variants - R510X and 2282del4 - mutations of the skin barrier gene encoding filaggrin (FLG) as very strong predisposing factors. [38] FLG, a filament aggregating protein, binds keratin intermediate fibers to the envelope of the stratum corneum cells and facilitates terminal differentiation of the epidermis. [38] Therefore, filaggrin is needed for the formation of skin barrier to maintain hydration and provide protection from environmental insults and infective agents. [40, 41] Recent studies have linked genetic FLG mutations to Th2 mediated AD and not non-Th2 inflammation AD giving rise to suggestions that skin barrier defect underlies the development of secondary allergic symptoms and respiratory atopy. [24] The degree of membrane disruption directly correlates with the severity of AD. [42]

The study by Pellerin et al. showed that the stratum corneum of lesional skin as well as the clinically nonlesional skin of adults AD patients has reduced expression of FLG and FLG-like proteins. [43] This was found to be as a result of nonsense mutations, proinflammatory cytokines and some defects in the proFLG processing. The study concluded that skin inflammation contributing to the AD-related epidermal barrier dysfunction is by downregulation of FLG and FLG-like proteins. FLG mutation has been identified as the most common genetic factor associated with AD and present in 15–50%. [44] However, 40% of FLG mutant gene carrier do not have AD. [38]

The epithelium in AD also have decreased barrier-stabilizing proteins such as loricrin (LOR), involucrin (IVL), and proline rich particles. [44] Tumor necrosis factor-alpha and interleukin (IL)-4 result in downregulation of LOR and filaggrin (FLG). [29, 45] In AD lesional skin, lipid synthesis is reduced [46] due to increased expression of enzyme stearoyl-CoA desaturase leading to increased unsaturated fatty acids and abnormal keratinization. [47] Th2 cytokines and IFN-γ also reduces long-chain free fatty acids (FFA) and ester linked-hydroxy (EO) ceramides in the skin membrane. [48, 49]

Many researchers have reported that defective skin barrier particularly in the epidermis preludes the pathologies seen in AD development mainly in the following ways: [26, 50–52].

- Defects in epidermal proteins such as FLG, keratins, transglutaminases, loricrin, involucrin reduces skin hydration and inflammatory thresholds while increasing skin pH, inflammatory cytokines, and allergen and microbes permeability. [26]
- Reduction in claudins increases transepidermal water loss (TEWL), reduces hydration, and allows allergens and microorganisms invasion. [53]
- Decreased long-chain FFA and ceramides increases TEWL and infections. [26]
- Decreased cathelicidin and human β-defensins increase microbial infections (mostly *Staph. aureus*) and pro-inflammatory cytokines. [26]

5.1.2 Immune system dysregulation

Polymorphisms of genes in the Th2 signaling pathway particularly cytokine receptors (IL-4R and IL-13R) are associated with immune dysfunction in AD. [54–57] Also implicated are genes transcribing for IL-31 and IL-33, thymic stromal lymphopoietin (TSLP) and its receptors (IL-7R and TSLPR), interferon regulatory factor 2, signal transducer and activator of transcription (STAT) 6, Toll-like receptor 2, and high-affinity IgE receptor (FcRI), [26, 54, 56, 58–60] vitamin D receptor and cytochrome P450 (CYP27A1 variant involved in D3 metabolism). [61, 62] Environmental factors (mostly allergens, microorganisms, smoke, and chemical irritants) also

cause modifications in DNA resulting in epidermal and genetic changes (epigenetic changes) without changing the DNA sequence of the corneocytes. [56]

Of recent, the skin epithelium was found to produce IL-25, IL-33, and/or TSLP (in response to extracellular molecules such as parasites and allergens) which activates skin group 2 innate lymphoid cells (ILC2). ILC2 produces IL-5, IL-9 and IL-13 which are Type 2 cytokines. [63] The T_H2 cytokines (IL-4, IL-13, IL-31) and T_H22 cytokine (IL-22) are believed to play roles in the overall pathogenesis of atopic dermatitis but mostly acute AD (**Figure 1**). [64–66]

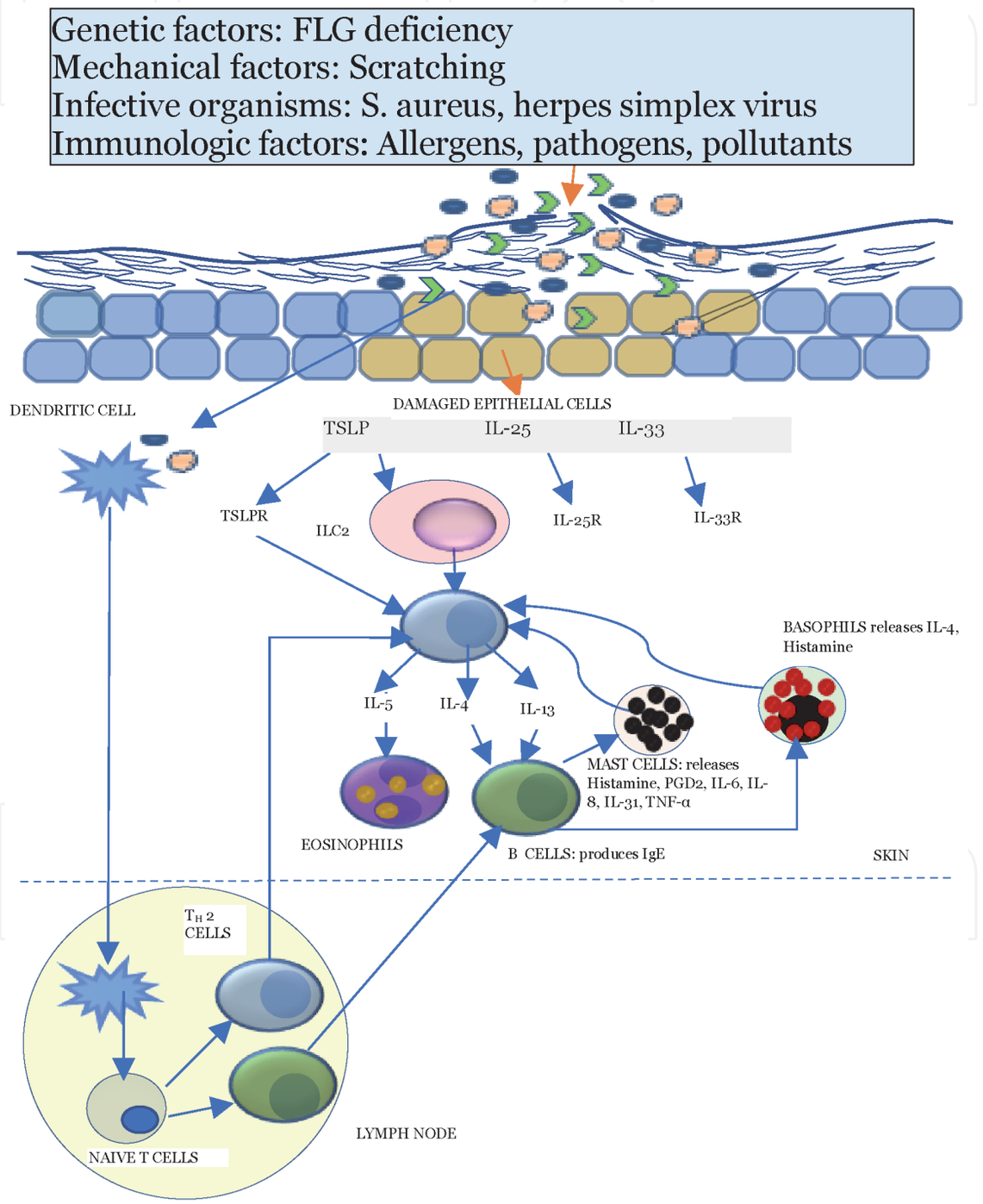


Figure 1.
Pathogenesis of atopic dermatitis. Damage to the skin barrier allows penetration of the skin by allergens, environmental factors and infective organisms activating the skin antigen-presenting cells (APCs). The APCs migrate to lymph nodes and stimulate naive T cells differentiation into TH2 cells and B lymphocytes. Damaged epithelial cells releases TSLP, TNF-α and IFN-γ and other TH2 cytokines (mostly IL-25 and IL-33) which induces mostly TH2 inflammation and subsequently keratinocyte apoptosis.TH2, T helper 2 cells; ILC2, innate lymphoid cell; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor. Cited from reference [100].

IL-4 is primarily produced by mast cells, Th2 cells, oesinophils and basophils. [67] IL-4 stimulates both the humoral and innate immunity. It reduces the expression epidermal differentiation complex (EDC) genes which regulates keratinocytes function. It activates B cell production which ingests antigens and presents them as major histocompatibility complex (MHC) II molecules to which T cells bind leading to cytokine production and signals to other phagocytes. The T cells further stimulate these activated B cells and differentiation into plasma cells leading to antibody production. IL-4 enhances the development of Th2 cells, suppresses the formation of major terminal differentiation proteins by downregulating the encoding genes for FLG, LOR, and IVL, increases fibronectin, and increases adhesion of *S. aureus* to the skin. [64, 68–71]

IL-13 acts similarly to IL-4 and these two are the most frequently produced cytokines by Th2 cells. IL-13 promotes tissue inflammation by inducing cellular migration (CD4+ T-cells, mast cells, eosinophils, and macrophages) to the dermis. [68, 71] Both IL-4 and IL-13 hinders keratinocyte differentiation resulting in membrane barrier dysfunction and increase periostin expression stimulating skin remodeling in chronic AD. [72, 73] They induce cytokines, epidermal dysfunction, suppress antimicrobial peptides (AMP), and stimulates allergic nflammation. [64, 74] Another study by Howell et al., [74] showed that filaggrin gene expression by keratinocytes stimulated by IL-4 and IL-13 was significantly reduced when compared with normal skin. [75]

IL-5 is produced by Th2, eosinophils and mast cells though eosinophils are the primary IL-5Rα-expressing cells. It functions as an eosinophil colony-stimulating factor, B-cells growth factor and increases immunoglobulin secretion – mostly IgA. [68, 76] IL-31, a cytokine mainly produced by CD4+ Th2 cells is a potent mediator of inflammation. [77] Monocytes, epithelial cells, and T cells have the receptor – IL-31R, on their cell membrane. [77] IL-31R induces and potentiates pruritus in AD [76, 78] by production of natriuretic peptide in the brain and chemokine release from keratinocytes. [79]

According to Rebane et al., IFN-γ is the characteristic cytokine induced by Th1 cells. [80] In acute AD, immunoglobulin G (IgG) inhibits the production of IFN-γ. [81] Interferon-gamma is secreted predominantly by activated lymphocytes such as CD4 T helper type 1 (Th1) cells and CD8 cytotoxic T cells. [82] Other cells producing IFN-γ are natural killer (NK) cells, B cells and antigen-presenting cells (APCs) – macrophages, and these cells aggregate in the skin during inflammatory reactions and infections. [83] Werfel et al., reported that CD8 T cells are part of the early cellular response in AD. [84] Higher CD8 IL-13+ 1CLA1 frequencies were seen in adults compared with children with AD. [85] CD8 T cells constitute 15% of allergen-specific T cells in the skin. [86] These cells stimulates the production of interferon-γ (IFN-γ), IL-13, and IL-22. [87–89] It was also reported that IFN-γ upregulated 3 apoptosis-related genes (*NOD2, DUSP1,* and *ADM*) and stimulates the overexpression of 8 genes (*CCDC109B, CCL5, CCL8, IFI35, LYN, RAB31, IFITM1,* and *IFITM2*) in keratinocytes of lesional skin.

TH17-associated molecules (IL-17A, peptidase inhibitor 3/elafin, and CCL20) are consistently upregulated in both patients with acute and chronic AD. IL-17 production is higher in intrinsic AD, and severe AD. [90] It reduces FLG and INV while stimulating antimicrobial peptide human beta-defensin 2 (HBD-2) in keratinocytes. [91, 92]

Apart from elevated IgE levels and eosinophilia, Leung reported that the peripheral blood has the following immunologic responses: [20].

- Increased basophil spontaneous histamine release
- Decreased CD8 suppressor/cytotoxic number and function

- Increased expression of CD23 on mononuclear cells
- Chronic macrophage activation, increased GM-CSF, prostaglandin E2, and IL-10
- Expansion of IL-4– and IL-5–secreting Th2-type cells
- Decreased numbers of IFN-γ–secreting Th1-type cells
- Increased serum sIL-2 receptor levels
- Increased serum eosinophil cationic protein levels
- Increased soluble E-selectin levels
- Increased soluble vascular cell adhesion molecule-1 levels
- Increased soluble intercellular adhesion molecule-1 levels

These immunologic changes underlies the skin inflammatory process in AD.

The cellular and cytokines infiltrates in the skin depends on the duration of the lesion. Cellular infiltrates particularly T cells occur as an immune response in AD patients. T lymphocytes are moderately increased in the dermal layer of nonlesional skin with marked increase in acutely inflamed areas and acute flares of chronic lesions resulting in epidermal cell apoptosis and spongiosis. Nonlesional skin has no eosinophils and macrophages, and cytokines seen are IL_4, IL-13 and IL_16 [20, 80] In acute lesional skin, cellular infiltrates consists of mostly T-cells, moderate amount of inflammatory dendritic cells (IDCs) mostly Langerhans cells, eosinophils, macrophages, IL-4, IL-13, IL-5, IL-22, IL-16, IL-31 and Granulocyte-macrophage colony-stimulating factor (GM-CSF). (20). Chronic lesional skin has mostly eosinophils and macrophages with moderate number of T cells, GM-CSF, and cytokines type are IL-4/13, IL-5, IL-12, IL-16, IL-31 and Interferon-γ. (20).

a. Acute Dermatitis: According to Grittler, AD is currently considered a biphasic disease depending on the type of cellular immune response to numerous environmental antigens and infections. [64] An initial phase of acute disease characterized by predominantly Th2 cells, as well as Th_H22 and few eosinophils progresses to a chronic disease and a switch to mostly Th1 cells, and Th17 cells. Th2 lymphocytes are the most predominant cells in all AD phenotypes, and play a key role in all allergic inflammation. [40, 93] Infiltration by Th2 cells are more in the acute phase than other phenotypes. These cells are targeted in immunotherapy for precision medicine. [94, 95]

b. Chronic Dermatitis: Allergen specific T-cell clone (TCC) from spontaneous chronic lesional skin of AD patients was found different from the TCC isolated from inhalant allergen patch test lesions. [86] These TCC are allergen-nonspecific cells that produce IFN-γ and the chronic changes seen in the skin and were found to be Th1 cells. [84] Many other studies also reported that Th1 cells increases in the lesions in chronic AD from an initial Th2 polarization. [96–98]

The Janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway acts downstream of more than 50 cytokines. [99] It is central to

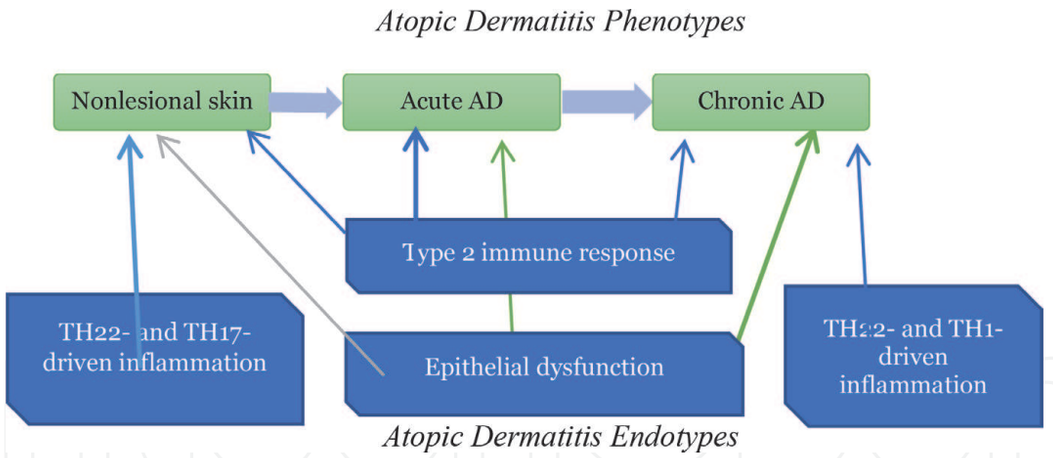


Figure 2.
Proposed atopic dermatitis Endotypes. Adapted from reference [100].

inflammatory processes involving B-cells, T-cells, neutrophils, macrophages and natural killer cells. Inhibitors of this pathway reduce are anti-inflammatory.

5.2 AD clinical phenotypes

AD has variable phenotypes that vary with age of onset, race, clinical course (acute or chronic), disease severity, therapeutic response, reactions to infectious agents, and allergic/irritant substances, IgE reactivity, and presence of other allergic diseases (asthma, allergic rhinitis, and food allergies). [94]

There are three main phenotypes of atopic dermatitis (**Figure 2**): (1) nonlesional skin, (2) acute AD, and (3) chronic remitting relapsing AD with acute flares. The underlying cellular and immune mechanisms in all three phenotypes are based on dysfunctional immune response as well as epithelial disruption. It is believed that underlying these complex clinical phenotypes are biomarkers that can be validated, and qualified for precision medicine for individualized treatment of AD. [100]

(2) non–type 2 immune response AD - with Th1-, Th17-, and Th22-induced inflammatory process and resultant epithelial dysfunction. [101–103]

5.3 Pathological markers

Disease assessment can be done pathologically. Biomarkers, such as CCL17, can be used for assessment of AD severity while filaggrin deficiency is being considered as a potential candidate for prognosticating the disease. Indoleamine 2,3-dioxygenase has been found useful as a predictive marker for viral skin infections [104].

5.4 Triggers for AD onset and exacerbation

Triggers are predisposing factors to AD episodes or flares. The control of these triggers are paramount in the treatment of AD. [105] and in improving the quality of life by maintain a disease free periods for the affected individuals or patients.

Atopic dermatitis may be triggered by microbial agents (common cold, secondary infection of lesions and skin infections), food (commonly due to eggs, milk, peanuts, wheat, soy, tree nuts, and fish and other sea foods), [106] aeroallergens (mostly house dust mites, molds, pollens, cigarette smoke, and animal dander), cosmetics, fragrances, weather (extremes of temperature and sweating), [106, 107] clothing such as wool [108], irritants, and sex hormones. [109] The two types of allergic reactions that can result from these triggers are – (1) Immediate allergic

reactions: IgE mediated type III with activation of the complement system, and (2) Delayed allergic reactions: due to activation of T lymphocytes and eosinophils. [110]

A. Microbial agents.

Dysfunctional adaptive immune response resulting in increased total and specific IgE levels, [111, 112] and innate immune system abnormalities such as reduced chemotaxis of cells to skin and antimicrobial peptide levels, Toll-like receptor defects [113] are the underlying factors contributing to skin infection and colonization. Disruption of the epidermal barrier facilitates microbial infection and colonization in AD patients. [114] The skin of AD individuals are highly predisposed to colonization or infection by various organisms most especially *Staphylococcus aureus* and Herpes simplex virus. [115]

The microbial organisms produce superantigens which stimulates marked inflammation. *S. aureus* has been implicated as a trigger of AD and as a factor responsible for chronic relapsing clinical course. [16] It releases toxins and superantigens that stimulates the innate immune response leading to T cells and macrophages production. It has been found in the skin of 80–100% AD individuals. [16] Specific IgE antibodies against staphylococcal enterotoxins corresponding to severity of the disease have been found in most AD cases. [16] The stimulation of chemokines such as TH2 cytokines IL-4 and IL-13 leads to reduced mobilization of human beta-defensin-2 (HBD-2) and impairs keratinocytes clearing of *Staph. aureus* while their neutralization significantly leads to clearance of the infective agent. [115–117] Apart from areas of infection, S aureus also colonizes normal-appearing skin in AD patients. [117]

Viral skin infections occur in AD patients more than other individuals without atopy. These infections may be localized or widespread. The most frequently seen viral infections are herpes simplex, warts and molluscum contagiosum. According to Damour et al., susceptibility is increased by overexpression of Th2 cytokines - IL-4, IL-13, IL-25, IL-33, and TSLP, low the AMP cathelicidin LL-37 and HBD-2 production; reduced IFN-γ, defect in cellular immune response by NK cells and dendritic cells. [115]

HSV may present as umbilicated vesicles, punched out erosions, impetigo-like lesions or secondarily infect atopic skin lesions. [115] Tzanck smear, PCR and viral culture can be used to confirm diagnosis. Also, fungi infection particularly *Malassezia sympodialis* has been found to contribute to chronic inflammation in AD, and it is associated with specific IgE antibodies against *M. sympodialis*. It was found to be more common in patients with head and neck type of AD.

B. Aeroallergens.

Aeroallergens are one of the most common environmental allergens causing AD flares or worsening. Many AD individuals have been found to have delayed hypersensitivity reactions to aeroallergens identified in their environment or reported by the patients while they have no reactions to aeroallergens which they had not been exposed to. Aeroallergens often producing delayed reactions with patch tests in adults AD are house dust mite, pollens (weed, grass and tree), and danders. [118] Adults with IgE sensitization to these aeroallergens have increased risk of developing persistent lesions of AD and other allergic diseases. [119] Control measures such as the use of allergen-impermeable mattress encasing, acaridae spray containing tannic acid and benzylbenzoate has been found to reduce the house dust mite antigen, Der p1. [120]

C. Food allergens.

Food allergy refers to an adverse immune-mediated reaction to ingested food product which is reproducible. [121, 122] Food intolerance is an undesirable non-allergic food reactions that does not involve the immune system (lactose intolerance). Prevalence of FA in adults is about 1–2%. [122] Some double-blind placebo-controlled oral food challenges (DBPCFCs) have shown that FA in adults AD are considerably lesser than in children, may not correlate with skin prick testing (SPT) or patch testing, and there may be little benefit to elimination diets. [123] However, a significant association has been reported between the IgE-mediated food allergy and severity of AD in adults. [124]

The immune reactions are of three types: [122].

a. IgE-mediated (immediate hypersensitivity reaction) - serum specific IgE antibody present with specific symptoms on ingestion of the food allergen within 2 hours. Symptoms include:

    i. Skin symptoms – itching of lips and/or eyes, eye redness, swelling of lips/tongue, urticaria, angioedema, flushing, rash, exacerbation of eczema;

    ii. Gastrointestinal symptoms – nausea, vomiting, diarrhea, pain and bloating;

    iii. Respiratory symptoms – nasal itching, rhinorrhea, sneezing, wheezing, dyspnea, or anaphylaxis;

b. Non-IgE-mediated (T-cell mediated with histological changes); (c) Combined reactions.

The skin is affected in 86% of food allergies and 38% respiratory system involvement. [121] The "priority antigens" which constitutes >90% of FA are dairy products, eggs (chicken), nuts (e.g., hazelnuts, walnuts, almonds, cashews, peanuts), soy beans, fish, crustaceans and shellfish, gluten foods (e.g., wheat, rye, barley), sesame and mustard. [121, 125] Less commonly: legumes, some fruits/juices (e.g., apple, grape), and vegetables (e.g., onions celery, carrots). [125] It is thought that raw food ingestion and food borne microbes may act as antigen. [126] This elicits immune responses by binding to immature gut villus, by increasing gut permeability, and by antigen transfer. [126] Food antigens produce anaphylactic reactions in sensitized individuals due to loss of oral tolerance to these antigens. [127].

Current therapies for FA entails strict avoidance of the offending food and allergen immunotherapy (AIT) - oral immunotherapy (OIT), sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) to ensure clinical desensitization, sustained unresponsiveness to allergens, and oral tolerance. [127] SLIT and EPIT are safer and more tolerable than OIT due to lesser ingestion of protein. [128]

6. Clinical features

6.1 Clinical symptoms and signs

Adult AD presentations are variable and differs by age, severity and course of the disease (acute or chronic course). It is a relapsing and remitting condition, with

episodes of disease exacerbation that occurs as frequently as two or three times per month. [13] Clinical symptoms and signs of adult/adolescent AD as reported by Liu et al., [129] in a multicenter study (42 dermatological centers) of 1605 AD cases over 12 years old (in decreasing percentages) are:

Pruritus (98.6), Xerosis (74.1), Associated environmental/emotional factors (73.9), Personal or family history of atopic diseases (61.4), Itching upon sweating (56.0), Flexural dermatitis (52.0), Facial pallor/facial erythema (35.5), Intolerance to wool (30.2), Eczema/AD before 12 years old (29.5), Scalp eczema/pityriasis (28.8), Urticaria/angioedema (26.8), Periauricular fissuring/eczema (25.8), Hand and/or foot dermatitis (24.7), Ichthyosis/palmar hyperlinearity/keratosis pilaris (23.3), Eyelid eczema (20.8), Eczema/AD history before 2 years old (20.2), Perifollicular accentuation (19.5), White dermographism (19.0), Nummular eczema (18.4), Pompholyx of hand/foot (17.2), Liable to skin infections (16.8), Anterior neck folds (16.7), Cheilitis (15.0), Perineum eczema (14.3), Orbital darkening (11.4), Pityriasis alba (9.5), Breast eczema (7.9), Recurrent conjunctivitis (7.3), Dennie–Morgan infraorbital fold (6.1), Anterior subcapsular cataracts (3.4), Keratoconus (1.3).

The characteristic sites of distribution of skin symptoms for adult AD are the hands, shoulders, neck, flexures, face and eyelids. The extremities and the trunk were less involved. [11] Adult AD characteristically presents as lichenified eczema on both extensor and flexural surfaces of the flexures, face, neck, shoulders and hands. In elderly adults, eczematous erythroderma is common. [4] Pruritus is a major symptom and major criteria in AD. It increases in the night.

6.2 Clinical patterns of adult AD

Three clinical patterns have been described by Heli et al. [130]

1. Chronic, persistent AD

2. Relapsing course

3. Adult-onset AD

Some classify the clinical features into (a) adult-onset AD, and (b) persistent AD and AD with relapsing course grouped together as persistent/recurring infantile or childhood AD. [131] In the elderly, AD can occur as geriatric onset AD, geriatric recurrence of typical childhood AD, and geriatric recurrence and /or continuation of adult AD. [10]

Persistent AD – refers to childhood AD running a chronic recurrent course up to and even in adulthood; occurs in 20–30% childhood cases. [131] Presentations are similar to children with flexural involvement (flexor surface of extremities) in majority of patients with pre-adult-onset. [132] The flexures are the areas initially involved. The flexor surface of arms and legs are also more highly involved than other body areas in these patients than those with adult-onset adult AD. [132] Affected cases usually have diffuse, lichenified, symmetrical lesions in the flexures mostly with facial eczema, dirty neck, and variable involvement of hands, limbs and trunk. Dirty neck, and vitiligo-like lichenified lesions in the flexures are signs of chronicity. [133–135]

Relapsing AD – this refers to childhood AD with complete resolution before or during adolescence, and recurrence in adulthood; occurs in about 12.2% cases of childhood AD. [131] Adult AD cases are prone to contact hand eczema while few with contact eczema have AD. According to Salvador et al., many of these patients have

chronic hand eczema as a result of atopy precipitated by irritant substances (heat, dust, soaps, etc) at work places or jobs causing wet hands. [131] This is often confused with contact irritant dermatitis and it is difficult to distinguish the two. [131, 136–138]

Adult-onset AD – In a study by Son et al., the body-site distribution of areas initially involved showed that the head and neck areas are the sites initially affected at the onset in adult-onset AD in contrast to flexural areas in pre-adult-onset AD. [132] The trunk was the most common area affected while flexural surfaces of arms and legs are the most affected area in persistent AD. [132]

From the study by Tanei et al., the senile-type AD usually have involvement of the face and neck, trunk, lichenification in flexural and extensor surfaces of arms and legs. [139] The antecubital and popliteal surfaces are less affected. Cases with moderate to severe eczema have other features of AD: erythroderma particularly on the face (atopic red face), loss of lateral eyebrows (Hertoghe sign), facial pallor, dirty neck (eczema with reticulate, ripple, or poikilodermic pigmentation), goose skin and Dennie–Morgan infraorbital folds. [139]

Tanei [140], described 3 types of lichenification in the antecubital areas of elderly patients with AD:

a. Localized lichenified eczema in the elbow fold;

b. Diffuse lichenified eczema in the elbow fold and flexure site of the arm;

c. Lichenified eczema around the scarcely involved elbow fold (reverse sign).

In the elderly, the classical type of localized lichenified eczema at elbow and knee folds is less common than the reverse type where lesions are around unaffected folds.

6.3 Clinical assessment of AD in adults

Assessment of AD should be done to determine the appropriate treatment as well as monitor response to therapy. SCORAD – SCORing Atopic Dermatitis – is a clinical tool for assessing the severity (extent/spread, intensity, and symptoms) of atopic dermatitis both objectively and subjectively. [141, 142] It was developed in 1993 by the European Task Force on Atopic Dermatitis to provide a consensus approach to AD management and useful in both children and adults. [143] Intensity of the symptoms was giving a weight of 60% and 20% each was allocated to spread (extent) and subjective signs (insomnia, itch). [144]

It consists of 3 components – A (Area or Extent), B (Intensity), C (Subjective symptoms). The formula for obtaining the total AD score of an individual is A/5 + 7B/2 + C. Area is expressed as a percentage of the whole body using the rule of 9 with a maximum value of 100%. Intensity has a maximum of 18 from a score of 6 for each of redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), and dryness (assessed in an area where there is no inflammation). Subjective symptoms are itch or sleeplessness assessed on a scale of 0–10 for each with a maximum 20.

7. Diagnostic criteria

Reports of AD in adults are not common and the clinical features are not categorical. However, the diagnosis of atopic dermatitis (AD) is based on its clinical symptoms regardless of age or sex of the individual. According to Tada [8], in the review of AD diagnostic criteria, the first concept of AD was described and published in 1933 by Wise and Sulzberger. [145]

Major criteria (3 or more needed for diagnosis):
1. Pruritus 2. Typical morphology and distribution 3. Flexural lichenification in adults 4. Facial and extensor involvement in infants and children 5. Dermatitis - Chronically or chronically relapsing 6. Personal or family history of atopy (asthma, hay fever, atopic dermatitis)
Minor criteria (3 or more needed for diagnosis):
(1) Xerosis (2) Ichthyosis/palmar hyperlinearity, keratosis pilaris (3) Immediate (type I) skin test reaction (4) Elevated serum IgE (5) Early age of onset (6) Tendency toward cutaneous infections (especially staph. Aureus and herpes simplex), impaired cell mediated immunity (7) Tendency toward non-specific hand or foot dermatitis (8) Nipple eczema (9) Cheilitis (10) Recurrent conjunctivitis (11) Dennie-Morgan infraorbital fold (12) Keratoconus (13) Anterior subcapsular cataracts (14) Orbital darkening (15) Facial pallor, facial erythema (16) Pityriasis alba (17) Anterior neck folds (18) Itch when sweating (19) Intolereance to wool ad lipid solvents (20) Periofollicular accentuation (21) Food intolerance (22) Course influenced by environmental and emotional factors (23) White dermographism, delayed blanch

Table 1.
Hanifin and Rajka diagnostic criteria for atopic dermatitis.

The first diagnostic criteria published was in 1961 by Rajka. [8] Both Hanifin and Rajka modified and combined their criteria in 1980 to form the most commonly used criteria (**Table 1**), [146] and many dermatological societies have also developed their criteria for this condition. According to Tada, the diagnostic standard by Hanifin and Rajka is useful in AD diagnosis in children and it also remains useful in adults as well. It has 6 major and 23 minor criteria.

According to the UK Working Party on AD in childhood, to qualify as a case of atopic dermatitis, the individual must have an itchy skin condition plus three or more of the following: history of flexural involvement, a history of asthma/hay fever, a history of a generalized dry skin, onset of rash under the age of 2 years, or visible flexural dermatitis. This has a sensitivity of 85% and specificity of 96%. [147] AD can consequently be diagnosed mainly by clinical symptoms and signs.

8. Complications

- Impetigo contagiosa
- Eczema herpeticum
- Molluscum contagiosum
- Erythrodermic eczema
- Ocular complication (keratoconus, cataract and/or retinal detachment)
- Kaposi's varicelliform eruption

9. Differential diagnoses

Differentials of adult-onset AD are seborrheic dermatitis, allergic contact dermatitis, cutaneous T-cell lymphoma, polymorphous light eruption, actinic prurigo, and

psoriasis, prurigo simplex, scabies, miliaria, ichthyosis, xerotic eczema, hand dermatitis (non-atopic), psoriasis, immunodeficiency diseases, collagen diseases (SLE, dermatomyositis), Netherton syndrome. In children, scabies, tinea corporis, seborrheic dermatitis, nutritional deficiency and allergic contact dermatitis are close differentials. [148]

10. Investigations

Investigations for AD are rarely required. Most investigations are carried out to identify triggering factors where applicable. A skin prick test is used for food and aeroallergen sensitization. Extracts or fresh food, and aeroallergens can be tested by placing them directly on the skin, which is then pricked through the liquid. This can also apply for local foods, which can be crushed with saline and similarly tested. The 'prick-prick test' can also be used by pricking the food with a lancet and then pricking the skin. The test site is observed in 15–20 minutes and the wheal reaction measured and recorded. A positive control with histamine should be ≥3 mm and a negative control is done with normal saline. [149] Patch tests are performed to diagnose allergic contact dermatitis (ACD); or a worsening dermatitis as a result of ACD to a constituent of the topical treatment. [150] Patch test is done for superimposed allergic contact dermatitis; in cases of suspected hand dermatitis. The highly specific atopy patch test is used to diagnose type IV hypersensitivity reactions.

Skin biopsy is usually required when there is erythroderma and a need to identify the underlying etiology. Histological findings can be suggestive of AD; however, they are not reliable for making a diagnosis. Total serum IgE levels are not specific for AD and does not correlate with disease severity. It is elevated in 50% of cases of AD.

In adult AD, colonization with *Staphylococcus aureus* is high and adult skin is more heavily colonized with Malassezia yeasts. [4] A positive ImmunoCAP assay for Malassezia species may be carried out. [149] This can then be treated with appropriate oral therapy. Swab tests can be carried out where necessary for secondary bacterial infections. Other tests are carried out appropriately based on other associated findings from the history or clinical examination.

11. Management

A very important part of management of AD is the education and counseling of all AD patients. With good understanding of the disease and what aggravates it, disease control can be achieved with the right skin care plan and an understanding of how to manage the flares. Successful management requires identification, elimination and prevention of specific identifiable and non-identifiable trigger factors. Managing AD requires a multispecialty approach which involves the dermatologist, allergologist, psychologist and nutritionist. Treatment regimens are usually based on the severity of the condition (**Table 2**). Evaluation and treatment according to ETFAD/EADV Eczema task force 2020 consensus paper is useful in routine clinical practice for AD in adults. [7] Patients should be educated on all available therapeutic options and they must actively participate in choosing the best option for themselves and their circumstance. Treatment regimens should be discussed and explained to individuals and their families to ensure adherence and compliance. Expectations, limitations, therapeutic options and prognosis are key to the overall management of AD.

Topical treatment.

The use of emollients is required both during an acute phase and as maintenance therapy as it forms the cornerstone of treatment for all types and severity of AD.

General measures	Mild	Moderate	Severe
Educate patients	Mildly potent TCS	Moderately potent TCS	Potent TCS
Emollients	TCIs	Crisaborole	Short course: OCS
Bath oils	Crisaborole	Wet wrap therapy	Short course: Cyclosporine A
Avoid triggers		NB-UVB/PUVA1	Biologics: Dupilumab
Antihistamines (Sedating type)			Long course: azathioprine, MMF
Antibiotics			Phototherapy: PUVA1
Bandages			

Table 2.
The treatment recommendations according to severity in adult AD.

Therapeutic baths in salt-rich water, colloidal oatmeal, wet –wrap dressings and topical antibiotics play an important role in this part of AD treatment.

Topical corticosteroids (TCS) are mainly used during a flare (**Table 3**). There are various potencies and dosages which are used based on severity of AD. TCS are used in active disease for up to 4 weeks and then 2 to 3 times weekly for preventive treatment. Topical calcineurin inhibitors (TCIs) are recommended for maintenance. Tacrolimus is more effective than pimecrolimus, and has been shown to be effective and well tolerated. [150–152] TCIs suppresses calcineurin which stimulates the expression of interleukin 2 (IL-2), a cytokine that regulates the T cell response. TCIs inhibit mast cell and neutrophil activation, basophil, eosinophil, and Langerhans cells functions.

Crisaborole, a topical phosphodiesterase-4 (PDE-4) inhibitor which downregulates the T-cell signaling pathways by inhibiting cAMP degradation is effective in reducing skin inflammation. [153]

Other forms of topical therapy include therapeutic baths in salt-rich water or colloidal oatmeal; diluted bleach baths and wet –wrap dressings and topical antibiotic when required.

Phototherapy can be used for moderate to severe AD, particularly where topical therapy has failed. Narrow band UVB in combination with medium dose UVA is

Severity	Eruption	TCS application
Severe	Primarily severe swelling/ edema /infiltration or erythema with lichenification, multiple papules, severe scales, crusts, vesicles, erosion, multiple excoriations and pruriginous nodules	Use of very strong or strong rank TCS is the first-line treatment. Strongest rank TCS are also available for refractory pruriginous nodules if sufficient effects are not achieved by applying very strong rank TCS
Moderate	Primarily moderate erythema, scales, a few papules and excoriations	Use of strong or medium rank TCS is the first-line treatment
Mild	Primarily dryness, mild erythema and scales	Use of strong or medium rank TCS is the first-line treatment
Slight	Primarily dryness with negligible inflammation	Topical application of medicines other than TCS (emollients)

Table 3.
Severity of eruption and topical corticosteroid (TCS) application. TCS, topical corticosteroid. [cited from Japanese guidelines for atopic dermatitis 2020. https://doi.org/10.1016/j.alit.2020.02.006, an open access article under the terms of the http://creativecommons.org/licenses/by-nc-nd/4.0/].

effective. [154–156] This mode of treatment however does have long term adverse effects (skin malignancies), and may not be available in all settings.

Systemic treatment (Dosages and side effects cited from Megna et al.) [157].

AD is being recognized as a systemic disease with atopic and nonatopic comorbidities. This plays an important role in the subsequent management and therapeutic implications for this condition.

Systemic therapy is required for chronic, severe cases, resistant cases, and when topical therapy has failed to control the disease. These include antihistamines, oral corticosteroids, immunosuppressive drugs and biologics. Combination of both topical and systemic is indicated for severe and resistant cases. [157]

Antihistamines may help to reduce itching. [158] Hydroxyzine and diphenhydramine hydrochloride provide a certain degree of relief but are not effective without other treatments.

Erythromycin, clarithromycin or cephalosporins can be used for 7–10 days for widespread bacterial skin infections. They are not recommended for use where there is no evidence of clinical infection as staphylococcal organisms are known to colonize the skin of AD patients. Systemic antifungals - itraconazole and ketoconazole – useful for cases with *Malassezia sympodialis* infection. [159]

1. Non-biologic drugs (Immunosuppressant and other)

    a. Oral corticosteroids (OCS) are effective for short term treatment for acute flares (**Table 2**) OCS rapidly improve the clinical symptoms of AD and are best used for short courses up to 1 week. [157] Long term use of oral steroids is not recommended because of the well-known side effects associated with them. These include hypertension, gastric ulcers, osteoporosis, diabetes and Cushing syndrome; as well as a rebound flare which can occur when they are abruptly stopped. They should be tapered to avoid relapse and rebound of AD. [157, 159–161] Dosage: Varies with type, AD severity, and comorbidities). Important Side effects: Diabetes, hypertension, skin atrophy, gastric ulcer, osteoporosis, glaucoma, pigmentary changes on prolonged use, and Cushing syndrome.

    b. Cyclosporine is the most widely used and first choice of systemic agents for the control of AD not responding to topical therapy. It is an immunomodulatory drug that inhibits interleukin by selective inhibition of cytokine transcription in activated T lymphocyte. Those on cyclosporine require close monitoring to avoid common side effects (nephrotoxicity, tremors, hypertension, electrolyte imbalances, etc.). Baseline tests and regular monitoring is required; particularly their renal status. Cyclosporine remains the only approved drug for systemic treatment of adult AD. Dosage: 2.5 to 5 mg/kg/day. Important Side effects: Nephrotoxicity, Hypertension, nausea, diarrhea, headache, paresthesia and myalgias.

    c. Methotrexate is effective in the treatment for moderate to severe AD. AD control be achieved with at a low dose for prolonged periods without any significant risk to the patient. It is a relatively safe drug. [162] Dosage: 5–25 mg/week. Important Side effects: Liver dysfunction, gastrointestinal complaints, hematological abnormalities, fatigue, and headache.

    d. Azathioprine is a purine synthesis inhibitor that reduces leukocyte proliferation. Various studies have been carried out with varying results.

It is used off label in situations where cyclosporine is contraindicated, or there has been no response. Dosage: 2–3 mg/kg twice a day. Important Side effects: Gastrointestinal disturbances, liver dysfunction, and leucopenia.

e. Others:

i. Mycophenolic mofetil (MMF) - Dosage: MMF:1000–2000 mg/day; EC-MPA enteric-coated mychophenolate sodium: 1440 mg/day. Side effects: Gastrointestinal disturbances, liver dysfunction, fatigue, hematological abnormalities and flu-like syndrome.

ii. Alitretinoin - Dosage: 30 mg/day. Side effects: Headache, TSH elevation, teratogenicity

2. Biologics

This class of pharmacological agents are engineered to target specific mediators of inflammation. Over the past decade, studies have reported the efficacy of targeted therapy blocking cytokines or mediators which play a role in AD pathogenesis. [163] According to Deleanu et al., based on mechanism of action, novel biologic therapies are classified into: anti IL-4 (Dupilumab) and anti-IL-4/IL-13 agents (Lebrikizumab, Tralokinumab), IgE directed therapy (Omalizumab), IL-22 blockers (Fezakinumab), anti-IL-12/23 (Ustekinumab), IL-31 directed therapy (Nemolizumab), thymic stromal lymphopoietin directed therapy (Tezepelumab), phosphodiesterase inhibitors (Apremilast, Crisaborole), and JAK inhibitors (Tofacitinib). [163]

a. Rituximab (anti-CD20) is a monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. [157] It reduces the expression of IL-5 and IL-13 by lowering B cell activation of T-cells. [164] Data on its use in adult patients with severe AD is limited. [157, 165] Dosage: 500–1000 mg iv (2-cycle infusion 2 weeks apart). Side effects: Headache, fever, nausea, diarrhea, weakness, flushing, muscle or joint pain, increased risk of infection, hematological abnormalities

b. Dupilumab, (anti-CD20) is a human monoclonal antibody that targets the shared α subunit of the IL-4 and IL-13 receptors, effectively blocking Th2 immune response. It is the only biologic drug licensed for treatment of adult AD. Clinical trials (Phase I-III) demonstrated its efficacy, as well as good patient and clinical reported outcomes using the SCORAD, IGA, DLQI and EASI assessment tools and health related quality of life (HRQoL) measures. [166] Long term use and safety profile still need to be established from ongoing studies. Dosage: 300 mg every 1–2 weeks. Side effects: Increased risk of infection, headache, and gastrointestinal disturbances.

c. Others:

i. Interferon-γ and infliximab have been used in severe AD and there are limited studies on their use. [163–165]

ii. Ustekinumab (anti IL-12, IL-23) 45 mg for patients ≤100 kg; 90 mg for patients >100 kg; at weeks 0 and 4 then every

12 weeks. Side effects: Headache, myalgia, increased risk of infection, fatigue, injection site reactions.

iii. Omalizumab (anti-IgE): Dosage: 150–600 mg every 2–4 weeks Side effects: Increased risk of infection, injection site reactions, headache

3. Small molecules

Apremilast is a new drug involved in modulation of multiple anti-inflammatory pathways targeting phosphodiesterase type IV (PDE4) inhibition. Apremilast downregulates pro-inflammatory transcription of several cytokines such as TNF-α, IFN-γ, IL-2, IL-5, IL-8 and IL-12. [163] There are limited studies and data on its use in AD. Dosage: 20–30 mg twice a day. Side effects: Headache, nausea, diarrhea.

Ultraviolet (UV) therapy [157] has the following functions:

- reduces the number of epidermal nerve fibers and expression of axon guidance molecules reducing itching,
- upregulates production of FoxP3-positive regulatory T cells thereby reducing AD severity
- inhibit DNA synthesis hence keratinocyte proliferation,
- suppresses antigen-presenting cells such as Langerhans' cells,
- induces T lymphocyte apoptosis and
- suppresses anti-inflammatory mediator production

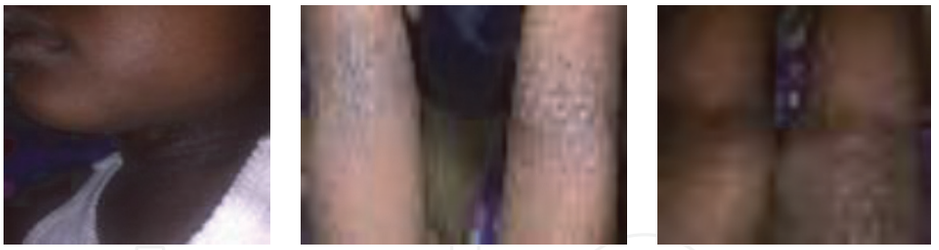
It is often used as second-line treatment for moderate-to-severe AD, resistant/relapse, chronic and poor topical response cases.

Broadband useful in adult AD: UVB (290–320 nm), narrow-band (NB) UVB (311–313 nm), excimer laser (308 nm), UVA-1 (340–400 nm), psoralens and UVA (PUVA), and combined UVA/UVB (280–400 nm).Narrow-band UVB radiation and medium-dose UVA1 are the most effective and safe for short and long term treatment.. Medium-dose UVA1 is the only type used in acute flares. Therapy is usually thrice weekly. Known side effects are nausea, fatigue, headache, itching, skin burns, blistering, erythema, irregular pigmentation, photodamage, actinic keratosis, and herpes virus reactivation as well as a higher risk of skin cancer, premature photoaging and skin cancers.

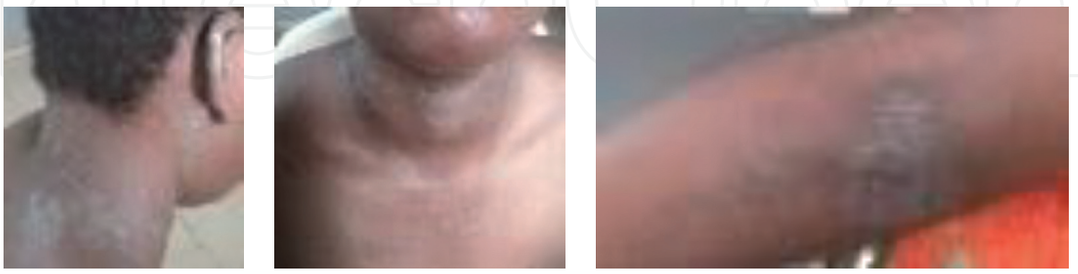
12. Conclusion

There is a worldwide increase in Adult AD with no standardized guidelines for its management. This condition greatly affects the quality of life of individuals and side effects from some of the drugs further limit the long term use of some forms of treatment. Biologic therapies are likely to change the course of the disease: decrease exacerbations, increase flare free periods and improve the quality of life. International guidelines therefore need to be developed based on further research on systemic immunotherapy options.

13. Pictures



Atopic Dermatitis in a male child with flexural involvement.



Atopic Dermatitis in a young adult female with involvement of head, neck, and extensor surfaces of elbows.

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