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Atopic dermatitis - the review

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by a disrupted epidermal barrier, immune dysregulation, and genetic predisposition. Affecting individuals across all age groups, AD presents with recurrent flare-ups and varying clinical patterns depending on age. The pathophysiology involves key elements such as loss-of-function mutations in the filaggrin (FLG) gene, overproduction of cytokines like IL-4 and IL-13, and skin colonization by Staphylococcus aureus. Management strategies include patient education, topical therapies (e.g., corticosteroids, calcineurin inhibitors, crisaborole, and tapinarof), systemic treatments like dupilumab and methotrexate, and phototherapy for refractory cases. Preventive measures, including breastfeeding and probiotic supplementation, offer limited benefits, emphasizing the need for individualized approaches. Innovative therapies and further research into AD pathogenesis hold promise for more effective disease control and improved quality of life for patients.

Keywords

atopic dermatitis, skin disorder, skin barrier dysfunction, immune dysregulation

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that, for a long time, was considered a mild condition predominantly affecting children in highly developed countries. However, it is now recognized that AD is prevalent in both developed and developing nations and affects individuals across all age groups. AD is characterized by a complex, multifactorial etiology involving immune system dysregulation, impaired skin barrier function, alterations in the skin microbiota, and genetic predisposition[1–4]. The disease course typically alternates between periods of remission and exacerbations[1]. Common clinical manifestations include skin irritation, erythema, and pruritic eczematous lesions. In some cases, bleeding and erosions may develop, further diminishing the quality of life for patients. Despite this, symptoms often show a tendency toward spontaneous resolution. Bacterial and viral superinfections are frequently observed[5], exacerbating discomfort, pain, and cosmetic concerns. Moreover, individuals with AD have a higher prevalence of comorbid conditions such as asthma, allergic rhinitis, and food allergies[6,7]. The pathogenesis of AD remains incompletely understood, reflecting its complexity. Nonetheless, ongoing research continues to uncover novel insights, paving the way for innovative therapeutic approaches aimed at improving disease management and patient outcomes.

Epidemiology

The epidemiological assessment of atopic dermatitis (AD) is complex, primarily due to its chronic and recurrent nature and the absence of objective diagnostic tests, resulting in variability across study findings[7–9]. Additionally, in many regions, particularly those with

limited medical infrastructure, reliable data on both the prevalence and severity of AD are scarce[5]. During a conference on the global aspects of AD held in 2023, the following insights were highlighted: in 2019, at least 2.23% of the global population - approximately 171 million individuals - were affected by AD[5]. The majority of cases are classified as mild to moderate, and the prevalence is consistently higher in females across all age groups[5]. The highest incidence occurs in childhood, with a typical peak in the 5–9-year age range. In studies conducted in the United States, the prevalence of AD in the pediatric population was reported at 24% among children aged 0 to 5 years[7,10]. Among these, 58% of cases were classified as mild, 39% as moderate, and 3% as severe[7]. The prevalence of AD demonstrates an upward trend in developing countries, whereas some nations with initially high incidence rates have reported stabilization or decline, potentially indicative of a "plateau" effect attributed to industrialization and the adoption of Western lifestyles[5]. Data on morbidity and mortality associated with complications, such as severe bacterial and viral superinfections, streptococcal glomerulonephritis, cellulitis, and eczema herpeticum, remain limited[5]. Further research is essential to understand the full burden of AD and its associated complications globally.

Pathophysiology

The pathophysiology of atopic dermatitis (AD) is intricate and multifactorial, with the mechanisms underlying the disease development interlinking[6] and reinforcing one another, creating a “vicious cycle”[11]. Key contributing factors include immune system dysregulation, impaired skin barrier function, genetic predisposition, altered skin microbiota, and environmental influences[7,12]. A healthy epidermal barrier serves as protection against physical, chemical, and microbial challenges[7,11]. In AD, the skin barrier becomes permeable, leading to increased transepidermal water loss, dehydration, and lesion formation[7,13]. Allergens can penetrate these compromised areas, reaching deeper skin layers and amplifying dysregulated immune responses[6,11], particularly the overproduction of cytokines such as IL-4 and IL-13[14].

Compromised Skin Barrier:

The stratum corneum, the outermost skin layer, consists of terminally differentiated keratinocytes called corneocytes[11]. Their functionality and adhesion depend on the proper structure and quantity of structural proteins (keratin, filaggrin, loricrin, and involucrin) and

lipids (fatty acids, cholesterol, and ceramides)[11]. Filaggrin (FLG) is a critical structural protein associated with AD, and mutations in the FLG gene that result in structural or quantitative abnormalities are strongly implicated in the disease[7,14]. FLG plays an essential role in shaping epidermal cells and positioning cytoskeletal components[4,11]. Its degradation generates acids that help hydrate the stratum corneum[11,14]. Loss-of-function mutations in the FLG gene are major genetic risk factors for AD[4,11,14]. These mutations disrupt lipid transport, reduce the availability of FLG monomers, and diminish levels of natural moisturizing factors derived from FLG metabolites[11,14]. Such changes lead to alterations in skin pH, lipid imbalance, and increased cell apoptosis[11,15]. IL-4 and IL-13 downregulate the expression of FLG, loricrin, involucrin, keratins 1 and 10, and elongases, which are enzymes involved in fatty acid chain elongation[11,16]. Simultaneously, these cytokines stimulate collagen synthesis, resulting in skin remodeling and lichenification over time[11]. Additionally, IL-4 and IL-13 enhance the expression of 3β-hydroxysteroid dehydrogenase-1 and androgens, which decreases triglyceride levels in sebocytes and keratinocytes, further exacerbating damage to atopic skin[11].

Dysregulation of Immune Response:

The immunological profile of AD is dominated by Th2 lymphocytes, which produce cytokines such as IL-4, IL-13, and IL-31 (known as "itch cytokine"[17]), alongside elevated IgE levels[11]. A compromised skin barrier facilitates the entry of environmental allergens, activating antigen-presenting cells such as inflammatory dendritic epidermal cells (IDEC), triggering an allergic response[11]. This cascade results in excessive stimulation of Th2 lymphocytes to secrete IL-4 and IL-13 - key cytokines in AD pathogenesis[11]. These cytokines drive the transformation of B lymphocytes into plasma cells, which subsequently produce allergen-specific IgE antibodies[11]. Additionally, cytokines contribute to neurogenic pruritus by directly stimulating cutaneous sensory neurons[11]. Another critical immune pathway in AD involves the Janus kinase (JAK) - dependent mechanism[7,11]. Among the four JAK kinases, JAK1 plays the most pivotal role in mediating IL-4 and IL-13 signaling[11]. Other JAKs primarily phosphorylate signal transducer and activator of transcription (STAT) proteins, including STAT6. STAT6 polymorphisms are associated with elevated IgE levels and an increased risk of AD[11]. STAT6 regulates the expression of GATA3, a transcription factor essential for Th2 lymphocytes, and facilitates IgE class switching in B cells[11].

Skin Microbiome:

Studies have shown that individuals with AD exhibit a reduced abundance of the natural protective skin microbiota, predominantly *Staphylococcus epidermidis*, compared to healthy individuals[11,17,18]. This depletion allows opportunistic pathogens to invade deeper skin layers, activating immune responses[11]. Skin lesions in AD further facilitate colonization and proliferation of pathogens, particularly *Staphylococcus aureus*[6,7,14]. This bacterium secrete toxins - like δ-toxin and α-toxin - and stimulates keratinocytes to produce proteases that degrade the skin barrier[17]. These processes drive Th2 lymphocytes to produce IL-4 and IL-13, which suppress antimicrobial peptide production[11], exacerbating epidermal damage and dysbiosis and perpetuating the "vicious cycle."

Clinical Presentation

Lesions in atopic dermatitis (AD) are most commonly observed in the elbow creases, popliteal folds, neck, face, and wrists. Over time, frequent scratching may result in lichenification, characterized by thickening of the skin in the affected areas[17]. AD is classified into three primary subtypes, distinguished by the age of onset, each with unique clinical features:

- Infantile Type: this subtype manifests before the age of 2, with acute lesions predominantly appearing on the face, cheeks, and scalp. These lesions typically present with erythema, swelling, and small vesicles, often accompanied by serous exudate[17].
- Childhood Type: this form occurs from the age of 2 through adolescence. Lesions are more localized, and the chronic nature of the disease results in skin that may become thickened, dry, and rough. Lesions are primarily confined to flexural areas of the body[17].
- Adult Type: in post-adolescence, AD is characterized by chronic eczema, with lesions predominantly affecting the hands, scalp, neck, and upper torso[17].

Triggering Factors

Recent studies have identified various environmental factors as significant triggers for flare-ups in individuals with atopic dermatitis (AD). Key contributors include air humidity,

elevated temperatures, and increased concentrations of particulate matter, mold, and other allergens[19,20]. Additionally, direct skin irritants, such as detergents and disinfectants, play an important role. During the COVID-19 pandemic, heightened use of these agents was associated with an increase in AD cases and symptom exacerbations[19]. Tobacco smoke also adversely impacts the integrity of the skin barrier. Both active and passive exposure to tobacco smoke have been linked to a higher prevalence of AD in children. Tobacco smoke inhibits the secretion of the anti-inflammatory cytokine IL-10, particularly in response to benzene, further contributing to disease pathogenesis[11]. Dietary changes associated with a more "Westernized" lifestyle have been implicated not only in the onset of AD[1,19] but also in worsening disease severity[11]. A direct correlation has been observed between the consumption of highly processed foods and the intensity of AD symptoms[11].

Treatment

Patient education, along with the education of close relatives, plays a pivotal role in the management of atopic dermatitis (AD), particularly in pediatric cases[7]. Healthcare providers, including family physicians, dermatologists, allergists, and pediatricians, should offer comprehensive information about the underlying causes, nature of the disease, its symptoms, strategies for early recognition, and effective management[21]. Highlighting the generally favorable prognosis of AD is crucial[21]. However, the chronic nature of the condition, persistent itching, and potential cosmetic concerns may necessitate tailored psychological support to address the emotional and social impact on patients[21,22].

Topical Treatment:

Since atopic dermatitis (AD) is a chronic condition, regular treatment and consistent skin care are paramount[21]. Fragrance-free emollients with high lipid (ceramide) content and low water content should be used regardless of symptom severity[14,21]. These emollients help maintain the moisture and integrity of the epidermal barrier, reduce symptom severity, and prolong the intervals between flare-ups[14]. Emollients should be applied once or twice daily and, during flare-ups, up to three times a day with more generous application[21]. Among the most effective emollients for reducing transepidermal water loss are occlusive formulations containing substances like petroleum jelly or paraffin, which create a hydrophobic barrier on the skin surface to prevent moisture evaporation. Additionally, humectants, which are hygroscopic

substances, attract and retain water in the skin, promoting optimal hydration and elasticity[21]. The choice of emollient type should be tailored to the climate, humidity, and environment where the patient resides, irrespective of AD severity. However, the form of the product (e.g., gels, ointments, creams) should align with the patient's individual preferences[14]. To optimize efficacy, baths should be limited to 10 minutes and followed by emollient application within three minutes to lock in moisture[21]. While there are no strict guidelines regarding bath frequency, it is essential to thoroughly cleanse the skin and remove debris. Alkaline soaps and other products that disrupt the skin's natural pH should be avoided in favor of hypoallergenic, low-pH, fragrance-free cleansers[21].

Topical Corticosteroids (TCS) are a cornerstone in the management of eczema in AD. Their selection should be based on matching the potency of the steroid to the severity of the symptoms and the specific body area affected[14]. Potent corticosteroids like clobetasol propionate should be reserved for short-term use during flare-ups to achieve clinical improvement, as prolonged use carries a risk of adverse effects. Sensitive areas of the skin, such as the face, neck, armpits, groin, and flexural surfaces, are more prone to steroid-related side effects such as skin atrophy, telangiectasia or hypopigmentation[6,14]. Therefore, mild corticosteroids like hydrocortisone or dexamethasone are preferred for these regions. A proactive approach is recommended, involving the application of mild corticosteroids once or twice a week to areas prone to flare-ups, even in the absence of active inflammation[14,21]. This strategy aims to prolong remission periods, reduce the frequency of acute episodes, and minimize the need for intensive treatments. Formulations should also be matched to the lesion type: lotions and gels are suitable for vesicular or exudative lesions, while ointments are ideal for thick, dry skin, such as on the hands and soles. Creams, due to their versatility, are appropriate for most skin types and areas[21].

Calcineurin inhibitors, such as tacrolimus and pimecrolimus, offer an alternative to corticosteroids. These agents exhibit potent local anti-inflammatory and immunomodulatory effects, reducing the risks associated with long-term steroid use[21]. They are particularly beneficial in cases of steroid resistance, patient reluctance to use steroids, steroid-induced skin atrophy, and for lesions in sensitive areas, including the face, armpits, groin, genital region, and skin folds[14]. For the treatment of atopic dermatitis, pimecrolimus is suited for mild to

moderate forms of the disease, whereas tacrolimus is designated for severe cases[14]. Similar to corticosteroids, a proactive regimen applying these inhibitors twice weekly can be beneficial[6,14]. The most commonly reported side effects include transient burning and stinging sensations[21].

Crisaborole is a non-steroidal, phosphodiesterase-4 (PDE4) inhibitor that reduces inflammation by suppressing pro-inflammatory cytokine production[21]. Approved for the treatment of mild to moderate AD in adults and children as young as 2 years[21] (or 3 months, depending on the country[23]), crisaborole has a favorable safety profile[14,23]. Like calcineurin inhibitors, it does not cause skin atrophy and is safe for sensitive skin, with no restrictions on treatment duration. Crisaborole is particularly useful in cases where corticosteroids or calcineurin inhibitors are contraindicated[23]. It can be used as monotherapy or in an alternating regimen with TCS to mitigate corticosteroid-associated side effects[23]. The primary adverse effect is localized burning at the application site[23].

Janus Kinase (JAK) Inhibitors, such as ruxolitinib[24], have shown promise in AD management. Ruxolitinib cream is approved for short-term, intermittent use in adolescents and adults (≥12 years) with mild to moderate AD[7]. Clinical trials demonstrated significant reductions in AD severity, pruritus, and improvements in sleep and quality of life, with rapid onset of symptom relief[21].

Tapinarof is a nonsteroidal anti-inflammatory agent with high efficacy and safety for moderate to severe AD in adults and children from 2 years of age[25]. It significantly reduces symptoms like itching, improving patients' quality of life. Due to minimal systemic absorption, tapinarof carries no risk of systemic side effects, making it suitable even for young children with extensive skin involvement[25]. Tapinarof represents a promising alternative for long-term AD management.

Systemic Treatment:

Systemic treatment is primarily reserved for severe cases of atopic dermatitis (AD)[26] that fail to respond to topical therapy[21]. These medications often exert immunosuppressive effects, leading to numerous contraindications and careful patient selection.

Systemic glucocorticosteroids, although FDA-approved and effective for acute management, are rarely recommended for long-term therapy due to their potential adverse effects[21]. Short-term use may be appropriate in acute, severe cases to rapidly control significant flare-ups[14,19].

Dupilumab is a monoclonal antibody targeting IL-4 and IL-13 receptors, primarily approved for the treatment of moderate to severe atopic dermatitis (AD) mainly in adults. However, clinical studies have demonstrated its efficacy and acceptable safety profile in pediatric populations as young as 6 months of age[11,27]. Clinical studies have demonstrated a rapid reduction in disease extent and symptom severity, including pruritus and skin pain, as well as improvements in sleep quality and overall quality of life[6,14]. When used in combination with topical corticosteroids, dupilumab has shown exceptional efficacy[6]. The therapy is generally well-tolerated, with the most common adverse effects being ocular dryness and blepharitis[21]. It is considered a safe treatment option however, the costs of treatment are exceedingly high[14].

Methotrexate (MTX) is a widely used immunosuppressant in adults and children with moderate to severe atopic dermatitis (AD), where it is recommended as a third-line therapy option[17,21,28]. Its mechanism of action involves inhibiting dihydrofolate reductase, thereby blocking DNA, RNA, and purine synthesis[28]. Its utility extends to patients with comorbid autoimmune or rheumatologic diseases, addressing multiple conditions simultaneously[6]. MTX is contraindicated in pregnancy and in individuals planning to conceive[6]. To reduce toxicity, it is typically co-administered with folic acid[21].

Cyclosporine A (CsA), a systemic immunosuppressant and oral calcineurin inhibitor, is an effective treatment for severe AD, particularly in cases unresponsive to other therapies[29]. CsA suppresses cytokine production by inhibiting transcription factors in T lymphocytes, thereby modulating T cell activation and reducing the inflammatory cascade characteristic of AD[29]. Common adverse effects include hypertension and nephrotoxicity[21]. Studies have shown that cyclosporine is more effective than methotrexate during active pharmacotherapy; however, disease relapse rates are higher after cyclosporine discontinuation compared to methotrexate, which offers superior long-term disease control[30].

Mycophenolate mofetil (MMF) is an immunosuppressive agent that inhibits DNA synthesis by interfering with purine biosynthesis, targeting rapidly proliferating cells such as lymphocytes[31]. MMF considered viable options for patients with moderate-to-severe AD who do not respond to other treatment[6,21]. Common side effects include headaches, gastrointestinal symptoms, and infections[32].

Azathioprine, an inhibitor of purine synthesis, directly impacts DNA production[21] and reduces leukocyte proliferation and modulates T-cell, B-cell, and antigen-presenting cell functions[6]. Side effects include gastrointestinal issues, infection risk, bone marrow suppression and liver toxicity so regular lab monitoring is essential[33]. Azathioprine may be used off-label for severe pediatric cases, though supporting evidence is limited[7].

Current evidence does not support a definitive role for antihistamines, such as hydroxyzine or diphenhydramine, in alleviating pruritus or eczematous symptoms associated with AD[21]. Nevertheless, these medications may be beneficial for managing sleep disturbances caused by AD-related symptoms[14,21]. In such cases, short-term, occasional use of oral sedating antihistamines is recommended.

Other Treatment Options:
For cases of severe atopic dermatitis (AD) unresponsive to topical corticosteroids, phototherapy using UVB (narrowband or broadband), UVA, or UVA1 is recommended[6,21]. Treatment typically involves regular sessions conducted 2–3 times per week over several months[21]. Phototherapy not only alleviates symptoms but also reduces Staphylococcus aureus colonization[21], thereby preventing symptom exacerbation and minimizing the risk of secondary complications.

Prevention

The prevention of atopic dermatitis (AD) remains an active area of research. Given the predominance of pediatric cases, most studies and hypotheses focus on interventions during the neonatal and infant stages, and in some cases, even the prenatal period. Although numerous studies have been conducted, the variability in methodologies and results often

precludes the formulation of clear, definitive recommendations that significantly reduce the prevalence of AD.

One widely explored hypothesis has been the use of emollients as a preventive measure; however, more recent studies have refuted this idea. Furthermore, evidence suggests that combining emollient application with frequent bathing may actually increase the risk of developing AD[4]. Despite their lack of preventive efficacy, emollients remain a cornerstone of therapy for individuals already affected by AD[14]. Notably, emollients containing ceramides, intended for use from the first days of life, have shown somewhat more encouraging results in studies[4].

Research into the use of probiotics, prebiotics, and synbiotics for the prevention of AD in children and their mothers has yielded conditional recommendations. Probiotics are recommended for pregnant and breastfeeding women whose children are at increased risk of developing AD, as well as for direct use in at-risk infants[4]. For formula-fed infants, formulas enriched with prebiotics are recommended, although the benefits of this approach are considered moderate[1,4,11,34].

Specific preventive measures include BCG vaccination during the neonatal period[4,35], exclusive breastfeeding for at least the first three months of life in infants[4,36] and vitamin D supplementation during pregnancy, which has been associated with a reduced risk of atopic dermatitis (AD) in offspring[4]. However, recent studies suggest that the use of vitamin D supplements[1,4] or hydrolyzed formulas in early childhood, the timing of introducing complementary feeding[4,37], and maternal avoidance of potentially allergenic foods during breastfeeding do not significantly reduce the risk of AD in children[4]. Similarly, avoiding allergens such as house dust mites has not shown substantial preventive benefits[4,38].

Elevated exposure to nitrogen dioxide (NO_2) and ozone (O_3) has been correlated with a higher prevalence of atopic dermatitis (AD) in the general population[20]. Furthermore, maternal use of antibiotics[39] or albendazole[40] during pregnancy has been linked to an increased risk of AD development in their offspring[4]. It is important to note, however, that albendazole use in older children and adults does not appear to increase the incidence of AD in these populations[4,41].

Conclusions

Atopic dermatitis (AD) remains a significant challenge for both patients and healthcare providers. Its multifactorial etiology, involving complex immunological, genetic, and skin barrier-related factors, necessitates a comprehensive therapeutic approach. While current treatment strategies effectively alleviate symptoms and enhance patients' quality of life, a deeper understanding of the underlying mechanisms of AD is essential. Ongoing research and advancements in the understanding of AD pathophysiology hold promise for the development of more targeted and effective therapies. These innovations may pave the way toward achieving sustainable, long-term disease control in the future.

Disclosure

Author's Contribution

Conceptualization - Joanna Wrona; Methodology - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Software - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Check - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Formal analysis - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Investigation - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Resources - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Data curation - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Writing (rough preparation) - Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Aleksandra Wójcik, Karol Stępniak, Wiktor Telega, Kinga Wnuczek; Writing (review and

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