Review Article

Atopic Dermatitis Pathogenesis And Management: A Review Article

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ABSTRACT

Atopic dermatitis (AD) is a prevalent inflammatory skin condition that affects individuals of all ages, including children. It presents with persistent itching and rash that can significantly impair quality of life. The pathogenesis of AD is multifactorial, involving immune dysregulation, genetic defects in epidermal barrier proteins such as filaggrin, and environmental factors that exacerbate skin barrier dysfunction. Clinically, AD is characterized by recurrent eczematous lesions and increased susceptibility to infections. Traditional management includes topical corticosteroids and calcineurin inhibitors to control inflammation and pruritus. In more severe cases, phototherapy and systemic immunomodulatory agents are utilized. New therapies, such as Janus kinase inhibitors (e.g., abrocitinib, upadacitinib) and biologics (e.g., dupilumab), offer targeted options with improved safety profiles. The aim of this review is to provide a comprehensive summary of the underlying mechanisms of AD, highlight recent advances in understanding its pathophysiology, and discuss current and emerging treatment strategies that reflect the evolving landscape of AD management.

Keyword: Atopic Dermatitis, Immune dysregulation, Skin barrier dysfunction, Topical Therapies, Biological agents.

Introduction

AD is a chronic, relapsing, pruritic inflammatory skin disorder that affects individuals across all age groups [1]. It frequently begins in early childhood, with approximately 50–60% of cases presenting within the first year of life and nearly 90% by the age of five [2]. Despite a tendency to improve with age, up to 50% of children continue to experience symptoms into adulthood [3,4]. AD can also present in adults, with adult-onset cases accounting for approximately 26% of total cases [4].

The pathogenesis of AD is multifactorial, involving skin barrier dysfunction, immune dysregulation, and environmental influences [5]. Genetic abnormalities, particularly the loss-of-function mutations in the filaggrin gene, play a vital role in compromising the skin barrier, leading to increased transepidermal water loss and heightened sensitivity to allergens and microbes [5]. Environmental irritants and allergens further exacerbate the disease course, contributing to chronic inflammation and recurrent flares [6].

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Clinically, AD manifests with age-specific eczematous lesions, pruritus, xerosis, and lichenification, severely impacting sleep, productivity, and quality of life [2]. The persistent cycle of itching and scratching aggravates the condition, resulting in skin thickening and secondary infections [7]. The diagnosis is primarily clinical, relying on key features such as pruritus, characteristic lesion morphology and distribution, a chronic or relapsing disease course, and a personal or family history of atopy [6]. Management begins with skin hydration and barrier repair. Emollients are recommended for all severities of AD and should be used liberally to reduce flare frequency and maintain remission [7,8]. Topical corticosteroids remain the mainstay for treating flares due to their strong anti-inflammatory properties [9]. In sensitive areas like the face and flexures, topical calcineurin inhibitors (TCIs) such as tacrolimus and pimecrolimus are effective steroid-sparing options [9]. For moderate-to-severe or treatment-resistant cases, narrowband ultraviolet B (UVB) phototherapy is a recognized second-line option due to its safety and efficacy in reducing cutaneous inflammation [10]. Patients with compromised skin barriers are also more susceptible to colonization by Staphylococcus aureus, which contributes to disease exacerbation and may necessitate antibiotic use [11].

Review of Literature

AD Definition: AD is a long-term skin condition that causes inflammation and tends to flare up repeatedly, affecting individuals across age spectrums. AD is manifested as pruritic, dry skin with eczematous patches, it's part of a group of related conditions known as the atopic triad, which also includes asthma and allergic rhinitis. Its substantial impact on patient quality of life (QoL) is compounded by an escalating prevalence, underscoring the significant clinical and epidemiological importance of this condition [2,3].

Pathophysiology: The pathogenesis of AD is intricate and multifactorial, encompassing elements of barrier dysfunction, immune response alterations, IgE-mediated hypersensitivity, and environmental influences [12]. The foundation of AD pathophysiology lies in genetic predisposition, particularly involving the filaggrin gene located on chromosome 1q2. This gene, which is essential for the formation and maintenance of the skin barrier, resulting in a compromised stratum corneum. This impairment causes increased transepidermal water loss and heightened susceptibility to allergens and pathogens. Clinically, individuals with filaggrin gene mutations often experience more severe symptoms of AD, including persistent itchiness, inflammation, and a greater risk of skin infections. Additionally, the loss of filaggrin gene is associated with alterations in the skin microbiome, which can exacerbate AD symptoms and contribute to the development of other allergic conditions, such as asthma and allergic rhinitis. These mutations disrupt keratinocyte maturation, alter lipid composition, increase skin pH, and further promoting microbial colonization [5,12,13]. Additional structural components, including corneodesmosin and tight junction proteins, play vital roles in maintaining barrier integrity. Researches have shown that inflammatory cytokines, including Interleukin-4 (IL-4), IL-13, IL-22, IL- 25, and IL-31, downregulate corneodesmosin expression, and potentially exacerbating barrier dysfunction [14-15]. Immunologically, AD is marked by a dominant Th2 response, characterized by elevated cytokines like IL-4, IL-13, and IL-5, alongside increased IgE levels. Alterations in skin microbiota, particularly the overgrowth of Staphylococcus aureus, significantly contribute to AD progression. This dysbiosis triggers a cascade of events including keratinocyte protease production, inflammatory toxin release, and mast cell activation, collectively perpetuating barrier dysfunction and inflammation [16,17]. Dendritic cells play a crucial role by activating native T cells upon antigen encounter, facilitating their differentiation into Th1 and Th2 subtypes, which, aimed at fighting antigens, contribute to persistent inflammation and worsen barrier dysfunction. Elevated levels of thymic stromal lymphopoietin in the skin of AD patients further promote Th2 responses and impact keratinocyte function, highlighting a complex interplay of immune cells in the inflamed skin [18,19] Recent research has, also, identified skin-resident group 2 innate lymphoid cells as significant contributors to AD pathogenesis, as they produce type 2 cytokines like IL-5 and IL-13, leading to allergic inflammation [20]. Moreover, genetic variants in immune pathway genes can disrupt the T-helper type 2 signaling pathway, with increased levels of IL-4 and IL-13 diminishing filaggrin gene expression and exacerbating skin barrier defects. The role of filaggrin gene breakdown products in the first year of life is critical, as their levels are lower in certain facial areas, supporting the initial development of AD in childhood [15]. Extensive research has explored environmental risk factors for AD, with maternal exposures during pregnancy emerging as a critical focus [21]. Maternal factors such as stress, smoking, and antibiotic use demonstrate significant correlations with childhood AD, while omega-3 fatty acids and probiotics show potential protective effects [22,23]. Supporting the “hygiene hypothesis”, early microbial exposures may modulate immune responses and potentially mitigate allergic inflammation. Climate factors, pollution, and regional variations contribute to AD prevalence, with studies indicating lower rates among foreign-born U.S children and rural populations, potentially due to

diverse bacterial endotoxin and pathogen exposures. Notably, while some microbial interactions may be protective, others can heighten AD risk, underscoring the nuanced relationship between environmental factors and this inflammatory skin condition [22,24].

Diagnosis: AD is diagnosed through clinical observation using the Hanifin and Rajka criteria [3], alongside patient history. The Modified American Academy of Dermatology criteria further assist healthcare providers in precisely diagnosing and assessing the condition's severity [25,26].

Basic Clinical Presentation: The pattern and location of skin lesions vary with age and stage of disease. The actual appearance of skin lesions resembles other types of eczema, with distinct characteristics in different phases:

- Acute phase: Bright red inflammation, swelling, small fluid-filled blisters, weeping, and crusting.
- Chronic phase: Skin thickening (lichenification), scratch marks, raised bumps (papules), and nodules.

Hanifin and Rajka Diagnostic Criteria [3]:

To formally diagnose atopic dermatitis, patients must meet:

1. Three or more major criteria:
 - Intense itching (pruritus).
 - Typical pattern and distribution of rash:
 • Adults: Lichenification in flexural areas.
 • Infants: Face and extensor surface involvement.
 - Chronic or repeatedly recurring dermatitis.
 - Personal or family history of atopic conditions (asthma, allergic rhinitis, atopic dermatitis).
2. Three or more minor criteria from a comprehensive list including:
 - Dry skin (xerosis).
 - Elevated blood IgE levels.
 - Early age of onset.
 - Increased susceptibility to skin infections.
 - Hand/foot dermatitis.

Other significant indicators:

 - Skin features: Keratosis pilaris, ichthyosis, wool intolerance.
 - Facial features: Orbital darkening, Dennie-Morgan folds (extra fold below eyes), facial pallor/redness.
 - Other manifestations: Nipple eczema, cheilitis (lip inflammation), recurrent eye problems.
 - Environmental triggers: Sweating-induced itching, emotional factors affecting symptoms.
 - Immune responses: Food sensitivities, immediate skin test reactivity.

Diagnostic Confirmation:

- Skin biopsy will show characteristic eczematous patterns.
- For treatment-resistant cases, especially in children:
 • Fluorescent enzyme immunoassays.
 • Skin prick testing for specific IgE antibodies.

The Modified American Academy of Dermatology criteria includes [26] :

Essential features

- Itch.
- Eczema with typical morphology and age-specific pattern.

Important features

- Early age of onset.
- Atopy (personal or family history).
- Dry skin.

Associated features

- Atypical vascular response (i.e., facial pallor, white dermographism).
- Keratosis pilaris, palmar hyperlinearity, ichthyosis.
- Ocular and periorbital changes.
- Other regional findings.
- Perifollicular accentuation, lichenification, and excoriations.

This comprehensive approach to diagnosis combines observable symptoms, patient history, standardized criteria, and when necessary, laboratory testing to confirm AD and distinguish it from other similar skin conditions.

Differential diagnosis: AD manifests as various skin lesions resulting in a wide differential diagnosis, which are shown in (Table 1) [10].

Management Patient and Family Education: Educating patients and their families is crucial for understanding the progression of the disease and effectively managing symptoms to prevent exacerbations. Collaborative Educational Initiatives that integrate the expertise of dermatologists, allergists, pediatricians, psychologists, and nursing professionals have been shown to substantially improve the QoL for individuals affected by AD [3].

Moisturizers: The regular application of moisturizers is vital for treating mild AD and preventing flare-ups. Moisturizers serve as the cornerstone of AD treatment. They typically contain varying concentrations of emollients, humectants, and additional ingredients such as ceramides, urea, lactate, and salicylic acid. These components, which are natural lipids found in the stratum corneum, help to hydrate and repair the skin barrier, alleviating symptoms such as itching, dryness, flare-ups, and infections [27].

Trigger Avoidance: Research indicates that AD flare-ups may be seasonal, often coinciding with periods of low humidity and cooler temperatures. Individuals with AD are more susceptible to irritant and allergic contact dermatitis; therefore, it is advisable to avoid common allergens, including fragranced products [28].

Bathing Recommendations: To prevent dehydration of the epidermis during bathing, it is recommended to use hypoallergenic soap and maintain water temperatures between 27-30°C, limiting exposure to 5-10 minutes.

After bathing, the skin should be gently dried, and topical emollients should be applied immediately to damp skin. Antiseptic soaps or solutions should be avoided as they may cause skin irritation [29]. Some soaps contain added food ingredients such as hydrolyzed wheat protein, rice starch, and rice bran, which are intended to enhance skin barrier function. However, caution should be exercised when using these products on patients with AD, as exposure to environmental food allergens may heighten the risk of epicutaneous food sensitization, particularly in individuals with compromised skin barriers [30].

Topical Therapies

Corticosteroids: Topical corticosteroids are considered the primary therapeutic option for controlling AD exacerbations owing to their potent anti-inflammatory effects. Corticosteroids are available in seven distinct potency levels, from very low to ultra-high strength, and their selection should be individualized according to disease severity [7]. In standard practice, topical corticosteroids are administered twice daily until marked clinical improvement or lesion resolution is observed. The duration of treatment is generally two weeks or less, guided by clinical improvement. To reduce the risk of adverse outcomes, it is recommended to use the lowest effective potency corticosteroid for the shortest duration required to sustain symptom relief. Evidence supports a proactive management strategy involving the intermittent application of topical corticosteroids, typically once or twice weekly, to areas previously affected by inflammation in order to prevent recurrence [31]. Low-potency topical corticosteroids are preferred for regions susceptible to skin atrophy, including the face, neck, axillae, groin, and flexural areas. In instances of severe exacerbation, the use of mid- to high-potency corticosteroids for a maximum duration of two weeks is advised to facilitate prompt symptom alleviation [10].

Calcineurin Inhibitors (TCIs): TCIs offer an alternative treatment for AD and do not carry the risks of skin atrophy and adrenal suppression associated with topical corticosteroids. Tacrolimus (Protopic) and pimecrolimus (Elidel) are FDA-approved TCIs for AD treatment. Studies have shown that tacrolimus ointment significantly reduces itching in both adult and pediatric patients [32]. A recent study utilized a wrist movement monitor to assess nocturnal scratching in children with AD, revealing a marked reduction in self-reported itching and scratching after tacrolimus application [32]. When compared to pimecrolimus, tacrolimus demonstrates superior efficacy in alleviating pruritus associated with AD. It has also been shown to reduce itching more effectively than hydrocortisone and aclometasone diproprionate. The predominant adverse effects associated with topical TCIs are temporary sensations of burning, pruritus, and erythema, which may be alleviated by pre-treatment with 5% lidocaine gel. Overall, Tacrolimus has demonstrated efficacy in managing pruritus associated with AD in both acute and chronic settings [7].

Phosphodiesterase-4 (PDE4) Inhibitors: PDE-4 inhibitors, such as crisaborole (Eucrisa), serve as an alternative treatment option for mild to moderate AD. It's approved in Canada for patients aged three months and older, crisaborole ointment has demonstrated improvements in skin and itching scores in clinical studies and boasts a favorable safety profile. Common side effects include application site pain, discomfort, or erythema, with rare occurrences of infection. However, the higher cost of PDE-4 inhibitors compared to topical corticosteroids may limit their accessibility for some patients [33].

Antibiotics: Topical antibiotics are recommended when signs of infection, such as crusting, oozing, or pus, are present. Combination creams containing corticosteroids and antibiotics, such as fusidic acid/betamethasone valerate or fusidic acid/hydrocortisone, are available; however, the prophylactic use of topical antibiotics on AD lesions without signs of infection is not advisable [27].

Antihistamines

Antihistamines are mainly used to relieve itching, especially at night, and patients who suffer from significant sleep disruptions caused by itching might find short-term, occasional use of oral sedative antihistamines helpful. However, there are no established guidelines for their use in treating AD [34].

Systemic Therapy

Prominent systemic drugs for AD and their characteristics are shown in (Table 2) [34].

Systemic Corticosteroids: Systemic corticosteroids can be used during acute severe exacerbations of AD, typically at a dosage of 0.5 mg/kg/day for 1 to 2 weeks. While they may provide rapid relief, their use is generally limited due to potential side effects and the risk of relapse [35]. Topical corticosteroids should be administered to inflamed, erythematous, or pruritic skin lesions prior to the application of emollients. Incorrect sequencing, such as applying emollients before corticosteroids, can markedly diminish the therapeutic efficacy of the corticosteroid agent [36].

Conventional Systemic Treatments

Cyclosporine: This is often compared to systemic corticosteroids in terms of efficacy. According to Schmitt et al. [36], there was no statistically significant difference in initial response rates between prednisolone and cyclosporine; nonetheless, cyclosporine was associated with a reduced relapse rate during follow-up.

Table 1: Differential Diagnosis of AD [10]**.**

Disease	Distinguishing features
Seborrheic dermatitis	Greasy, scaly lesions, absence of family history
Psoriasis	Localized patches on extensor surfaces, scalp, buttocks; pitted nails
Neurodermatitis	Usually, a single patch in an area accessible to itching; absence of family history
Contact dermatitis	Positive exposure history, rash in area of exposure, absence of family history
Impetigo	Superficial skin infection caused by streptococci and/or staphylococci; begins as vesicles with thin, fragile roof
Scabies	Papules, finger web involvement, positive skin scraping
Systemic diseases	Findings on complete history and physical examination vary by disease
Dermatitis herpetiformis	Vesicles over extensor areas and associated enteropathy
Dermatophyte infection	Serpiginous plaques with central clearing, positive potassium hydroxide preparation

Table 2: Prominent systemic drugs for AD and their characteristics [34]**.**

Systemic Drugs for Atopic Dermatitis	Mechanisms (in Atopic Dermatitis)
Systemic corticosteroids	Glucocorticoids act by binding to and activating intracellular glucocorticoid receptors. When activated, glucocorticoid receptors bind to regions of DNA responsible for the promotion and activation of transcription factors, which then results in the inactivation of genes. Methylprednisolone is a powerful medication with anti-inflammatory properties and the ability to inhibit the immune system.
Cyclosporine	Cyclosporine has potent immunosuppressive properties. Cyclosporine inhibits cell-mediated reactions and T-cell-dependent antibody production. Cyclosporine inhibits the production and release of lymphokines including I- 2 at the cellular level.
Methotrexate	Methotrexate has the capacity to decrease inflammation and suppress an overactive immune system. Methotrexate is a folic acid antagonist, with antimetabolite properties. It inhibits DNA synthesis by the competitive inhibition of the enzyme dihydrofolate reductase.
Azathioprine	Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). Azathioprine is broken down into 6-MP and a methylnitroimidazole. The 6-MP is converted in the cell into several purine thioanalogs.
Mycophenolic acid	Mycophenolate mofetil has immunosuppressive properties. It is converted into mycophenolic acid which blocks an enzyme called “inosine monophosphate dehydrogenase”. The enzyme inosine monophosphate dehydrogenase is important for the formation of DNA in cells, especially in lymphocytes. Consequently, it reduces the rate of lymphocyte multiplication.

Dupilumab	Dupilumab is a monoclonal antibody. It is designed to block receptors for IL-4 and IL-13. It relieves symptoms by blocking receptors and preventing IL-4 and IL-13 from working. Patients suffering from AD have high levels of IL-4 and IL-13, which can cause inflammation of the skin leading to symptoms.
Abrocitnib	Abrocitinib blocks the action of JAK which have an important role in inflammation that occurs in AD. Abrocitinib reduces inflammation and itching of the skin.
Baricitinib	Baricitinib is an immunosuppressant medication and works by disabling the JAK which have an important role in the processes of inflammation and damage that occur in patients with AD. Baricitinib reduces skin inflammation and symptoms of AD.
Upadacinib	Upadacitinib has immunosuppressant properties and acts by blocking the JAK enzymes which are involved in the processes that lead to inflammation, and blocking them controls symptoms.

*AD: Atopic Dermatitis; IL: Interleukin; JAK: Janus Kinase

Table 3: Licensed JAK (Janus kinase) inhibitors [40].

Drug	Adult Dose	Pediatric Use	Onset (weeks)	Effectiveness	Common Side Effects	Pregnancy Use
Abrocitinib	100–200 mg once daily (OD)	≥12 years (same dosing)	1–2	Slightly better than baricitinib and dupilumab for itch and clinical signs	Nausea, acne, thrombocytopenia	Avoid
Baricitinib	4 mg OD (may reduce to 2 mg)	Not licensed	1–2	Slightly less effective than upadacitinib for itch and signs	Hypercholesterolemia, transaminitis, thrombocytosis	Avoid
Upadacitinib	15–30 mg OD	≥12 years: 15 mg OD	1–2	30 mg dose superior to dupilumab and abrocitinib for clinical signs and itch	Acne, anemia, neutropenia, transaminitis	Avoid

*Abrocitinib and upadacitinib are approved for adolescents ≥12 years. Effectiveness based on EASI(Eczema Area and Severity Index)-75 and pruritus reduction from network meta-analysis.

Methotrexate and Azathioprine: These conventional systemic treatments are utilized in cases where other therapies are insufficient. They can help manage inflammation over a longer term. Methotrexate functions as a folic acid antagonist, hindering processes such as cell division, DNA/RNA synthesis and repair, as well as protein synthesis, which collectively reduce immune system activity. While the precise mechanism of MTX in AD remains unclear, it has been suggested that it inhibits the Janus kinase (JAK)/STAT pathway. For many years, MTX has been utilized in managing moderate to severe AD. However, there have been only a few non-randomized controlled trials investigating its effects and treatment protocols. Azathioprine acts as a prodrug that undergoes rapid biotransformation in vivo to yield 6-MP after the cleavage of its imidazole moiety. Its principal immunosuppressive activity is thought to result from 6-MP-derived thioguanine nucleotides, which integrate into DNA and inhibit its replication and synthesis [13,37].

Interleukin Inhibitors: IL inhibitors target specific cytokines involved in AD. Notably, IL-13 has been identified as a key therapeutic target, leading to the development of monoclonal antibodies such as:

- Dupilumab: This medication binds to IL-4Rα, inhibiting both IL-4 and IL-13 signaling. It reduces inflammation and the sensation of itch [28].
- Tralokinumab and Lebrikizumab: Other monoclonal antibodies targeting IL-13, which may be effective for refractory cases of AD [28].

JAK (Janus kinase) Inhibitors: The JAK-STAT signaling pathway plays; a significant role in AD's pathogenesis. JAK inhibitors, such as upadacitinib and abrocitinib, selectively inhibit this pathway, leading to reduced pro-inflammatory cytokine activity. These inhibitors can improve disease severity, pruritus, and QoL, often with side effects that are more manageable than those associated with broader systemic treatments [38]. The FDA's approval of ruxolitinib marked the introduction of JAK inhibitors for skin disorders, with subsequent approvals for other agents. JAK inhibitors can be administered orally or topically, with topical forms having a lower risk of side effects compared to oral administration [39]. A decision aid of licensed JAK inhibitors can be found in (Table 3) [40].

Phototherapy:Phototherapy is an effective treatment option for generalized AD and pruritus, boasting a favorable safety profile. Various forms include: UVB and UVA Therapy. These modalities can reduce inflammation by affecting immune cell activity in the skin. PUVA therapy, combines psoralen with UVA to enhance treatment efficacy. The mechanisms behind phototherapy's effectiveness include the reduction of epidermal nerve fibers and the modulation of immune responses, such as decreasing IgE-binding and mast cells in the dermis [34].

Conclusion

AD is a complex inflammatory skin condition that significantly impacts patients' well-being. Its multifactorial pathogenesis involves genetic predisposition, immune dysregulation, and environmental factors. Topical corticosteroids remain the primary treatment, complemented by calcineurin inhibitors and phototherapy for refractory cases. Maintaining skin barrier integrity through regular emollient use is crucial in reducing flare-ups and minimizing pharmacological interventions. A multidisciplinary approach addressing both physical and emotional aspects is essential for optimal patient care. Ongoing research into AD's underlying mechanisms and potential therapies promises to improve patients' QoL, with future investigations focusing on identifying novel molecular targets and developing personalized treatment strategies.

Conflict of Interest

None

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