From itch to inflammation: Understanding eczema in the context of immune response

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Abstract

Atopic dermatitis (AD), commonly known as eczema, is a chronic and non-curable inflammatory skin disorder characterized by intense itching, redness, dryness, and rashes. It typically manifests during infancy or early childhood and can persist into adulthood. AD is closely linked to immune system dysregulation, elevated levels of immunoglobulin E (IgE), and a weakened skin barrier, making affected individuals more susceptible to skin infections and increasing the likelihood of developing asthma and allergies later in life—a progression known as the "Allergic March". Conventional treatment primarily involves moisturizers and topical corticosteroids; however, these are often associated with adverse effects. New therapeutic options such as topical calcineurin inhibitors and biologic agents targeting specific immune pathways have been introduced in recent years. Additionally, advancements in drug delivery systems have emerged to enhance the safety and effectiveness of treatment. This review aims to provide a comprehensive overview of the etiology, conventional and modern treatment approaches, and recent innovations in managing AD.

Keywords: Pathogenesis, Eczema, Emerging Nanotechnology

1. Introduction

Eczema, also known as atopic dermatitis (AD), is a common chronic immune-inflammatory disease characterized by itching, redness, xerosis, and eczematous lesions. About 80% of AD cases typically initiate during infancy or childhood, while the remaining cases emerge in adulthood. The acute stage of AD commences with a Th-2 cell-driven inflammatory response and elevated immunoglobulin E (IgE) levels, eosinophils, mast cells, and lymphocyte infiltration, reflecting immune system hyperactivation, which leads to erythema with ill-defined borders and intense pruritus. Chronic inflammation and immune dysregulation increase susceptibility to infections, particularly by Staphylococcus aureus (S. aureus), and AD is often the first step in the "Allergic March". Children suffering from AD may have a risk of developing asthma, allergic rhinitis, food allergies, and rheumatoid arthritis. This review aims to illuminate the underlying pathophysiological mechanism of AD and explore strategies for its management (1,2).

2. Pathogenesis

Eczema is a chronic inflammatory cutaneous condition with involvement of genetic, immunological, and environmental components. A prominent characteristic is dysfunction of the skin barrier, basically caused by mutations in the filaggrin (FLG) gene, which compromises the epidermis, enhances water loss, and facilitates entry of allergens and microbes.

Immune dysregulation is at the forefront of AD, characterized by a Th2-type response. Cytokines such as IL-4, IL-5, and IL-13 drive IgE production, eosinophil activation, and downregulation of barrier proteins. IL-31 has a strong association with itch, and IL-22 with thickening of the skin and disruption of the barrier. TSLP, an epithelial cytokine, drives Th2 inflammation, while Th1 (IFN-γ) and Th17 (IL-17) pathways are more prominent in chronic or severe forms.

Hormonal and neuroimmune mediators are Corticotropin-releasing hormone, histamine, prostaglandins, and leukotrienes, which increase inflammation and itch. Decreased antimicrobial peptides (AMPs) compromise skin barrier defense with Staphylococcus aureus colonization that further exacerbates inflammation by toxins and superantigens.

This dynamic interplay among cytokines, hormones, immune cells, and microbes sustains the inflammation-barrier dysfunction cycle and emphasizes the necessity for selective, multi-pathway therapies in AD (3–6). Figure 1 illustrates the pathogenesis of AD.

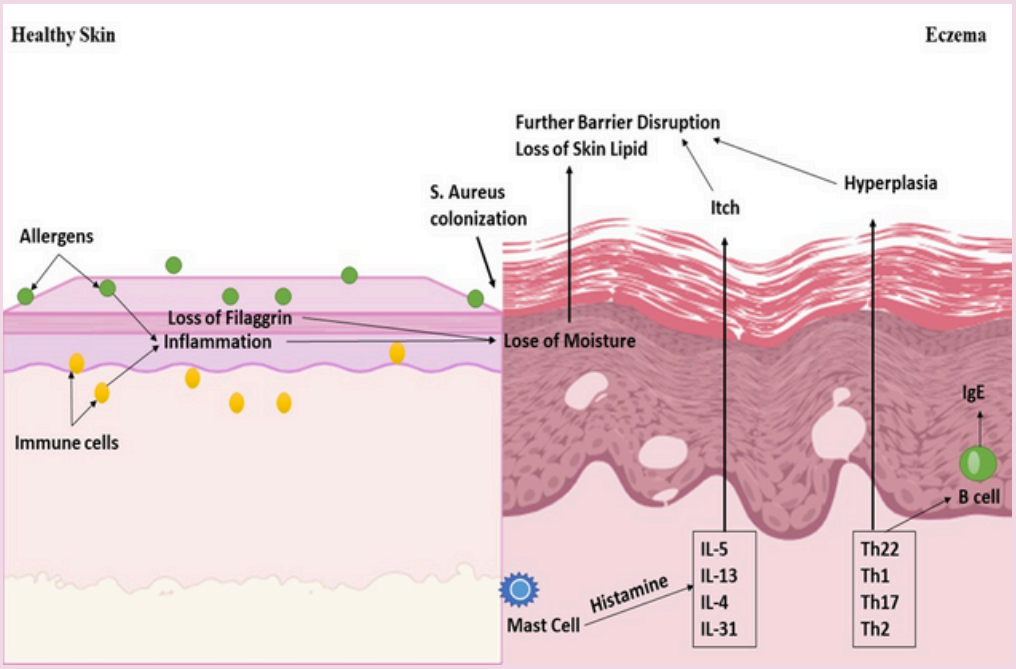

Figure 1. Pathogenesis of Eczema

3. Management

AD is a chronic inflammatory skin disease characterized by disrupted skin barrier, immune dysregulation, and increased sensitivity to environmental allergens. Conventional treatment relies on topical therapies that target barrier repair, inflammation, and itching. These treatments are, however, constrained by limitations in drug permeation, duration of action, side effects, and long-term efficacy, especially in severe or resistant disease (7). Emerging advances in drug delivery and nanotechnology offer new avenues for therapeutic enhancement, minimize side effects, and increase patient compliance. Table 1 discusses multiple intervention possibilities.

3.1. Traditional topical treatment

Emollients and moisturizers are still the pillars of AD management because they also hydrate the stratum corneum, decrease transepidermal water loss (TEWL), and maintain barrier integrity. Nonetheless, their inherent anti-inflammatory capacity is weak, particularly in moderate to severe disease. Topical corticosteroids (TCS) are the cornerstone of acute flares. TCS are graded according to potency and selected based on age, lesion location, and disease severity. Efficacious but potentially problematic with prolonged use is the worry of skin atrophy and hypothalamic-pituitary-adrenal axis suppression, which tends to result in "steroid phobia" and nonadherence (8,9).

Steroid-free topical calcineurin inhibitors like tacrolimus and pimecrolimus are alternatives for sensitive skin. They suppress T-cell proliferation and pro-inflammatory cytokines without thinning the skin. Although they have a black-box warning for carcinogenicity, real-world safety is excellent; however, they are costly and cause local irritation and, therefore, are restricted in use.

New topical medications have emerged that counteract the limitations of TCIs and TCSs. PDE-4 inhibitors crisaborole, reduce pro-inflammatory cytokines through increased levels of cyclic AMP. JAK inhibitors delgocitinib and tofacitinib inhibit over 60 cytokines in atopic dermatitis (AD) via the JAK-STAT pathway. These small molecules are effective against inflammation, serving patients refractory to first-line treatments. AhR agonists like tapinarof represent a new non-steroidal method of managing inflammation and enhancing barrier function.

Biologic agents such as dupilumab, tralokinumab, lebrikizumab, and nemolizumab have revolutionized the treatment of moderate-to-severe AD. Dupilumab suppresses IL-4 and IL-13, enhancing skin barrier and Th2 inflammation, and others suppress cytokines such as IL-13 and IL-31 to reduce pruritus. But these biologics are expensive and are reserved for resistant cases only (10–12).

Table 1. Management of AD

Category	Intervention	Description/Examples	Comments
1. Skin Barrier Repair	Emollients/Moisturizers	Petrolatum, ceramide-based creams, colloidal oatmeal, urea-containing products	Use liberally and regularly; essential for daily maintenance
2. Topical Anti-inflammatory Therapy	Corticosteroids (TCS)	Hydrocortisone (mild), betamethasone, clobetasol (potent)	First-line for acute flares; potency chosen based on severity and site
	Calcineurin Inhibitors (TCIs)	Tacrolimus, Pimecrolimus	Steroid-sparing; suitable for face, eyelids, intertriginous areas
	PDE4 Inhibitors (Newer)	Crisaborole	Mild to moderate eczema; reduces inflammation with minimal side effects
3. Systemic Therapy	Immunosuppressants	Cyclosporine, Methotrexate, Azathioprine	For moderate-to-severe cases unresponsive to topicals; require monitoring
	Oral Corticosteroids	Prednisone	Short-term use only; for severe flares
4. Biologic Therapy	IL-4/IL-13 Inhibitors	Dupilumab	First approved biologic; highly effective with long-term disease control
	IL-13 Specific Inhibitors	Tralokinumab, Lebrikizumab (under development)	New targeted agents under clinical trials
5. Small Molecule Inhibitors	JAK Inhibitors	Upadacitinib, Abrocitinib, Baricitinib	Oral agents; rapid action; monitor for systemic side effects
6. Antimicrobial/ Adjunctive Care	Topical/Oral Antibiotics	Mupirocin (topical), Cephalexin (oral)	For secondary bacterial infections due to scratching or barrier breakdown
	Antihistamines	Hydroxyzine, Cetirizine	Limited role; may aid sleep and reduce nighttime itching
7. Lifestyle & Supportive Measures	Allergen/Irritant Avoidance	Avoid harsh soaps, fragrances, wool, allergens	Individualized based on triggers
	Wet Wrap Therapy	Soaking skin and wrapping with damp and dry layers	Used during severe flares to enhance absorption of topical agents
	Education & Counseling	Skincare training, psychological support	Improves adherence, reduces anxiety, especially in pediatric patients
8. Emerging Therapies	Microbiome-based Treatments	Topical probiotics, bacterial transplantation	Experimental; aim to restore skin microbial balance
	Nanocarrier-based Drug Delivery	Liposomes, NLCs, ethosomes	Improve drug penetration and reduce systemic exposure

3.2. Emerging nanotechnology and novel drug delivery systems

To counteract the limitations of traditional treatment, drug delivery systems based on nanotechnology are currently leading the therapeutic revolution in AD. Such systems are engineered to enhance dermal penetration of drugs, extend drug retention at the point of inflammation, enable reduced dosing, and minimize systemic exposure. Diverse nanotechnologies for eczema management are outlined in Table 2.

3.2.1. Polymeric nanoparticles

Polymeric nanoparticles—especially those compounded with chitosan, PLGA, and Eudragit—have shown improved therapeutic performance in preclinical AD models. Corticosteroids (e.g., hydrocortisone) and natural antioxidants (e.g., hydroxytyrosol)-co-loaded systems substantially lowered TEWL, erythema, and cytokine levels in mice. Surface modifications with hyaluronic acid enhance epidermal adhesion and targeting. These systems provide sustained drug release, lower dosing frequencies, and improved tolerability by the skin over conventional creams (13).

3.2.2. Lipid-based nanocarriers

Lipid-based delivery systems like solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, ethosomes, and nanoemulsions possess high biocompatibility and resemble the skin's lipid matrix. Ethosomal gel formulations of tacrolimus and cyclosporine A exhibited enhanced drug penetration and deposition in deeper skin layers than commercial products. Further, nanoemulsions with skin-identical lipids, phytosphingosine, and linoleic acid not only provide effective drug delivery but also restore barrier function (14).

3.2.3. Gene-silencing nanocarriers (siRNA)

Cutting-edge strategies involve the delivery of small interfering RNA (siRNA) against transcription factors such as NF-κB or cytokines such as IL-13. Liposomal and polymeric vehicles have been effective in delivering these gene silencers in preclinical AD models, lowering mast cell infiltration, inflammatory signaling, and serum IgE. These methods have the potential for long-term disease modulation instead of the suppression of symptoms (15).

3.2.4. Inorganic nanoparticles

Inorganic nanocarriers (e.g., silver, zinc oxide, and silica nanoparticles) have exhibited anti-inflammatory and antimicrobial activity. Nevertheless, their therapeutic application is hampered by immunogenicity concerns and the risk of worsening AD symptoms. It has been shown that particle size and dose play a decisive role in both efficacy and safety, and strong design and toxicity testing requirements are needed (16).

3.2.5. Nanoparticle hybrids and intelligent delivery platforms

Hydrogel systems integrate hydrogels' moisturizing and calming effects with the sustained, targeted delivery of nanoparticles. Thermo- and pH-sensitive hydrogels provide controlled release of corticosteroids, herbal medications, and dual therapies to enhance bioavailability, skin retention, and irritation reduction—perfect for chronic AD control (17).

Intelligent delivery platforms extend this strategy by integrating nanoparticle-loaded hydrogels into wearable fabrics such as wet-wraps. Such systems ensure stimulus-responsive, on-demand release of drugs against inflamed or infected skin, ensuring precision therapy for acute and refractory AD(18).

Table 2. Nanotechnology-based delivery system for AD

Nanotechnology/Delivery System	Key Components	Mechanism/Features	Application in AD	Advantages
Lipid-Based Nanocarriers	Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs)	Encapsulate lipophilic drugs; enhance skin penetration	Delivery of corticosteroids, herbal actives	Enhanced skin permeation, reduced irritation, improved stability
Polymeric Nanoparticles	PLGA, chitosan, Eudragit	Controlled drug release; biodegradable matrices	Anti-inflammatory and immunomodulatory agents	Sustained release, targeted delivery, reduced systemic effects
Nanoemulsions	Oil-in-water or water-in-oil systems	High surface area; enhanced solubility of actives	Herbal extracts, essential oils, corticosteroids	Improved drug solubility, non-greasy feel, better skin absorption
Liposomes and Niosomes	Phospholipids (liposomes), non-ionic surfactants (niosomes)	Vesicular carriers; biocompatible	Delivery of calcineurin inhibitors, antioxidants	Skin targeting, minimized systemic absorption, enhanced drug stability
Hydrogel-Nanoparticle Hybrids	Thermo-/pH-responsive hydrogels with embedded nanoparticles	Dual-function: hydration + sustained release	Maintenance therapy, dual-drug delivery	Improved adherence, reduced irritation, prolonged contact time
Microneedle Arrays	Biodegradable or polymeric microneedles	Bypass stratum corneum, direct intradermal delivery	Biologics, peptides	Painless delivery, enhanced penetration, reduced dosing frequency
Smart Textiles (Wearable Platforms)	Wet-wraps infused with nanoparticle-loaded hydrogels	Stimulus-responsive drug release	Infected or inflamed AD lesions	On-demand release, tailored therapy, increased patient compliance

4. Future perspectives

Although the mainstay of AD treatment remains traditional topical therapies, their drawbacks have led to the development of more advanced drug delivery systems. Nanocarrier-based systems offer several advantages, including greater drug solubility, targeted distribution, long-lasting therapeutic effects, and increased patient compliance, especially in complex situations, including sensitive skin areas or steroid fear. A paradigm shift in the treatment of AD is being brought about by new developments in gene silencing, intelligent delivery methods, and polymeric, lipid-based, and hybrid hydrogel systems. To bring these developments from the bench to the bedside, translational research can focus on clinical proof of concept, large-scale production, and regulatory convergence in the future.

5. Conclusion

The drive to apply knowledge of AD in the creation of new medication has led to fruitful research and more treatment possibilities. Adopting a multidisciplinary approach improves disease management and quality of life. Developments over recent years have enabled better treatment outcomes to be achieved, especially in advanced AD. Nanotechnology drug delivery has the potential to enhance treatment in patients, opening the door to a new generation of safer, more compliant drugs.

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