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ATOPIC DERMATITIS IN ADULTS: EPIDEMIOLOGY, MOLECULAR PATHOPHYSIOLOGY, AND EVOLVING THERAPEUTIC LANDSCAPES

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Abstract: Atopic dermatitis (AD) is a chronic, relapsing, and heterogeneous inflammatory skin disease characterized by severe pruritus, xerosis, and recurrent eczematous lesions. Although traditionally regarded as a predominantly pediatric disorder, adult AD represents a substantial and increasingly recognized health burden, including persistent childhood disease and adult-onset disease. Its pathogenesis involves a complex interaction of genetic susceptibility, epidermal barrier dysfunction, immune dysregulation, and cutaneous microbial dysbiosis. In adult patients, barrier impairment is associated with age-related ceramide depletion, altered skin pH, abnormal protease activity, and reduced expression of tight-junction proteins, particularly claudin-1. Immunologically, acute disease is dominated by Type 2 cytokine signaling involving IL-4, IL-13, and IL-31, whereas chronic adult AD demonstrates additional Th1 and Th22 immune responses. Increased *Staphylococcus aureus* colonization and reduced microbial diversity further contribute to persistent inflammation and barrier disruption. Clinically, adult AD commonly affects flexural areas, the hands, and the head and neck and may present with lichenification, prurigo nodules, nummular eczema, and severe chronic pruritus, leading to sleep disturbance, psychological distress, and reduced quality of life. Diagnosis remains primarily clinical, with careful exclusion of allergic contact dermatitis, psoriasis, scabies, and cutaneous lymphoma in atypical cases. Management combines barrier repair, topical anti-inflammatory therapy, proactive maintenance, phototherapy, and systemic targeted treatments. Biologics and JAK inhibitors have expanded precision therapeutic options, while microbiome-based interventions and nanotechnology-assisted drug delivery represent promising emerging strategies. Improved adult-specific endotyping and biomarker development may facilitate more personalized and effective disease management.

Keywords: Atopic dermatitis; adult atopic dermatitis; epidermal barrier dysfunction; filaggrin; Type 2 inflammation; IL-4; IL-13; IL-31; *Staphylococcus aureus*; skin microbiome; JAK inhibitors; biologic therapy; precision medicine; pruritus; personalized treatment.

1. Introduction & Epidemiological Overview

Atopic dermatitis (AD) is a chronic, phenotypically heterogeneous inflammatory skin disorder characterized by severe pruritus, xerosis, and recurrent eczematous lesions. Although historically conceptualized as a predominantly pediatric condition that remits prior to adulthood, contemporary epidemiological data demonstrate that AD is a common and burdensome disease across the human lifespan, following a bimodal prevalence distribution peaking in early childhood and middle-aged adulthood. Globally, AD affects up to 10% of adults, with adult prevalence estimates consistently falling between 2% and 10% in developed nations and between 3% and 10% in the United States. In global health metrics, AD ranks 15th among all nonfatal diseases and first among all skin conditions in disability-adjusted life-years (DALYs), reflecting its substantial population burden. Epidemiological

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surveys indicate a clear female preponderance among adolescent and adult populations. Furthermore, the natural history of adult AD exhibits significant heterogeneity regarding age of onset [1,2]. While many adult patients suffer from persistent disease originating in early childhood, systematic reviews show that approximately 26.1% of adults with AD or one in four cases report adult-onset disease, developing clinical manifestations for the first time in adulthood. Adult AD is also associated with a substantial personal and economic burden, marked by frequent outpatient visits, increased emergency care utilization, and high rates of comorbid mental health conditions and atopic disorders such as allergic rhinitis and asthma [3,4].

2. Molecular Pathophysiology & Adult Endotypes

The molecular pathophysiology of adult atopic dermatitis (AD) involves a complex interplay between genetic predisposition, epidermal barrier impairment, adaptive and innate immune dysregulation, and cutaneous microbial dysbiosis. Unlike pediatric AD, where loss-of-function null mutations in the filaggrin (*FLG*) gene represent the primary genetic driver of early-onset severe disease, common *FLG* null mutations do not typically predispose individuals to adult-onset AD. Instead, adult-onset AD is genetically associated with alternative loci, including the 1903/A promoter polymorphism of the mast cell chymase (*CMA1*/*MCC*) gene—which correlates inversely with serum IgE levels—as well as polymorphic variants in the interleukin-4 receptor (*IL4R*) and the vitamin D receptor [5,6].

Epidermal barrier dysfunction in adults is further modified by age-related ceramide depletion, altered lipid chain lengths, and an elevated, basic skin surface pH. This alkaline shift over-activates desquamatory serine proteases, such as kallikrein-related peptidases (KLKs), leading to the premature degradation of corneodesmosomes and essential lipid-processing enzymes. Simultaneously, key tight junction proteins in the stratum granulosum—specifically claudin-1, claudin-23, and ZO-1—are downregulated, with claudin-1 deficiency demonstrating a direct inverse correlation with Th2-polarized inflammatory biomarkers like total serum IgE and peripheral blood eosinophil counts. Immunologically, while acute lesions across age groups feature a Th2-skewed axis producing IL-4, IL-13, and the pruritogenic cytokine IL-31, chronic adult AD undergoes distinct immunological remodeling. Adult AD transitions away from the Th17-dominant axis characteristic of childhood AD, acquiring prominent CLA+ Th22 helper (CD4+) and Tc22 cytotoxic (CD8+) T-cell subsets alongside an upregulated Th1 response marked by elevated IFN-γ expression in chronic lesional skin [8,9]. Microbiologically, adult AD skin exhibits marked bacterial dysbiosis, characterized by a heavy absolute burden of *Staphylococcus aureus* that significantly reduces microbial alpha-diversity. While non-lesional skin is predominantly populated by commensal coagulase-negative staphylococci (CoNS) such as *S. epidermidis* and *S. hominis*, lesional skin is heavily dominated by *S. aureus*, which secretes virulence factors—including phenol-soluble modulins (PSM-alpha, delta-toxin) and staphylococcal enterotoxins—that trigger alarmin release, mast cell degranulation, and chronic barrier collapse [10].

3. Clinical Phenotypes & Patient Burden in Adults

Adult atopic dermatitis (AD) presents with a highly heterogeneous, polymorphic clinical spectrum that differs markedly from pediatric manifestations. Whereas early childhood AD preferentially involves the facial and extensor surfaces, adult AD characteristically affects flexural skin folds, the hands, and the head and neck region. Morphologically, adult skin lesions frequently manifest as chronic, leathery lichenified plaques, prurigo nodules, nummular eczema, or papular lichenoid and follicular eruptions. Erythroderma, facial and eyelid dermatitis, hand eczema, and the Hertoghe sign (thinning or loss of the lateral eyebrows) are also significantly more common in adult

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populations. Pruritus remains the defining cardinal feature and primary complaint in adult AD, reported as the initial symptom in up to 87% of patients [11].

This persistent itch is accompanied by marked xerosis and significant skin pain resulting from excoriation-induced epidermal denudation, deep painful fissures, and underlying cutaneous inflammation. Consequently, chronic pruritus triggers severe sleep disturbances, including delayed sleep onset, frequent nocturnal awakenings, early morning awakenings, and daytime somnolence. Beyond cutaneous signs, adult AD confers a profound psychosocial and systemic burden. Patients exhibit elevated rates of psychological comorbidities, including major depressive disorder, generalized anxiety disorder, and suicidal ideation, largely driven by chronic sleep loss, social stigmatization, and unremitting itch. Furthermore, the disease imposes a major socioeconomic impact through high out-of-pocket medical costs—averaging $600 annually per person in the United States—frequent urgent or emergency healthcare utilization, lost workplace productivity, and absenteeism [12,13].

4. Diagnostic Evaluation & Differential Diagnosis

The diagnosis of adult atopic dermatitis (AD) remains fundamentally clinical, as no validated, specific laboratory biomarkers currently exist to establish a definitive diagnosis. Diagnostic criteria systems developed primarily for epidemiological and clinical trial standardization include the Hanifin and Rajka criteria—which require at least three major features (such as pruritus, typical flexural lichenification, chronicity, and a personal or family history of atopy) plus three minor criteria—and the UK Working Party criteria, which mandate an itchy skin condition alongside three or more minor clinical indicators [14].

In adult populations, particularly those presenting with adult-onset disease, establishing a correct diagnosis requires meticulous differentiation from mimicking dermatoses, including allergic contact dermatitis (ACD), cutaneous T-cell lymphoma (CTCL/Sézary syndrome), psoriasis, scabies, seborrheic dermatitis, nummular eczema, and eczematous drug eruptions. While skin biopsies are not routinely required for classic presentations, a selective punch biopsy with standard histopathological evaluation is strongly indicated for atypical or treatment-refractory lesions to exclude CTCL, psoriasis, or cutaneous lupus; histologically, AD characteristically demonstrates epidermal spongiosis, hyperkeratosis, and dermal perivascular mononuclear infiltrates with eosinophils [15]. Additionally, direct immunofluorescence of perilesional skin can be utilized to rule out autoimmune blistering disorders such as bullous pemphigoid. Patch testing using an expanded allergen series is highly recommended for adult-onset, recalcitrant, or atypical cases (such as isolated head, neck, eyelid, or hand dermatitis) to identify coexistent or mimicking ACD triggered by topical medications, emollients, or environmental haptens. Conversely, routine skin prick testing, total serum IgE measurement, and food allergy panels are generally not recommended for diagnosing adult AD, given that adult-onset disease exhibits significantly lower rates of systemic IgE sensitization compared to pediatric presentations [16,17].

5. Therapeutic Strategies & Precision Medicine

Standard management of adult atopic dermatitis (AD) begins with non-pharmacological baseline measures, including regular daily bathing in lukewarm water, avoiding alkaline soaps that elevate skin surface pH, and routine application of emollients to repair stratum corneum barrier defects and reduce transepidermal water loss (TEWL). While historical "humoralistic" doctrines discouraged active topical intervention due to fear of suppressing beneficial cutaneous elimination, contemporary clinical consensus emphasizes a structured step-care approach combining barrier maintenance with

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topical anti-inflammatory therapy [18]. Topical corticosteroids (TCS) remain the first-line reactive treatment for acute disease flares, applied once or twice daily according to lesion severity. However, continuous long-term TCS usage carries significant risks of cutaneous atrophy, epidermal thinning by up to 70%, striae, and severe rebound flares upon discontinuation. To mitigate steroid-associated adverse events and address widespread patient corticophobia, steroid-sparing topical calcineurin inhibitors (TCIs) specifically tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%) are indicated, particularly for sensitive sites such as the face, eyelids, neck, and intertriginous folds. In addition, the topical phosphodiesterase-4 (PDE4) inhibitor crisaborole suppresses intracellular inflammatory cascade activity without causing epidermal atrophy. To prevent recurrent relapses, proactive therapy consisting of twice-weekly maintenance application of low-potency TCS or TCIs to previously affected, clear skin effectively controls subclinical inflammation and reduces flare frequency [19].

For moderate-to-severe adult AD refractory to optimized topical therapies, targeted systemic biological therapies represent a major milestone in precision medicine. Dupilumab, a fully human IgG4 monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα) subunit, dual-blocks IL-4 and IL-13 cytokine signaling, thereby inhibiting the proximal drivers of type 2 inflammation. Systemic IL-4Rα blockade suppresses circulating biomarkers such as CCL17 (TARC) and total serum IgE, restores cutaneous alpha-diversity, and significantly reduces the absolute burden of *Staphylococcus aureus* colonization on both lesional and non-lesional skin. Clinical trials and meta-analyses demonstrate that dupilumab achieves substantial improvements in EASI scores, Investigator's Global Assessment (IGA) responses, pruritus, skin pain, and overall health-related quality of life. Beyond dual IL-4/IL-13 blockade, highly selective biologic agents targeting specific cytokines along the type 2 inflammatory axis include the IL-13 inhibitors tralokinumab and lebrikizumab, the IL-31 receptor antagonist nemolizumab (which directly targets central itch pathways), the anti-IL-22 antibody fezakinumab, the anti-IL-33 antibody etokimab, and the anti-thymic stromal lymphopoietin (anti-TSLP) antibody tezepelumab [20,21].

In parallel with biologic therapies, small-molecule Janus kinase (JAK) inhibitors including oral agents (abrocitinib, upadacitinib, baricitinib) and topical formulations (tofacitinib, ruxolitinib, delgocitinib)—inhibit the intracellular JAK-STAT signaling pathway, blocking signal transduction for multiple pro-inflammatory cytokines and rapidly alleviating chronic pruritus. Additional novel systemic targets under active clinical evaluation include sphingosine-1-phosphate (S1P) receptor modulators such as etrasimod and anti-OX40 monoclonal antibodies such as rocatinlimab. To optimize topical drug delivery, advanced nanotechnological formulations including solid lipid nanoparticles, polymeric nanoparticles, hyaluronic acid-decorated nanoparticles, and niosomal gels are being developed to enhance skin penetration and localized tissue retention while reducing systemic absorption. Finally, precision management in adult AD incorporates microbiome-directed strategies, such as targeted commensal skin transplants (e.g., coagulase-negative staphylococci) to suppress *S. aureus* superantigens, alongside strict avoidance of empirical food elimination diets, which lack efficacy in unselected adult populations and carry severe risks of nutritional impairment or triggering immediate-type anaphylactic reactions upon food reintroduction [22].

6. Conclusion

Atopic dermatitis in adults is a common, complex, and heterogeneous inflammatory skin disease driven by a multifaceted interplay of genetic predisposition, epidermal barrier impairment,

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adaptive and innate immune dysregulation, and cutaneous microbial dysbiosis. The transition from reactive, short-term flare suppression to proactive maintenance and endotype-targeted therapy represents a major advance in clinical management. Continued progress in adult-specific endotyping, biomarker validation, skin microbiome restoration, and advanced drug delivery promises to deliver highly effective, personalized treatments that minimize disease burden and restore quality of life for adult AD patients

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