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ATOPIC DERMATITIS: SKIN BARRIER DYSFUNCTION, TH2-DOMINANT IMMUNOPATHOGENESIS, DIAGNOSTIC CRITERIA, AND TARGETED BIOLOGIC AND SMALL-MOLECULE THERAPY

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ABSTRACT: Background: Atopic dermatitis (AD) is the most prevalent chronic inflammatory skin disease, affecting 15–20% of children and 1–10% of adults worldwide—representing more than 230 million affected individuals globally. Characterized by intense pruritus, skin barrier dysfunction, and relapsing eczematous lesions, AD profoundly impairs quality of life and is the leading cause of years lived with disability (YLD) among skin diseases. Recent decades have established AD as a complex immunological disorder driven by type 2 helper T-cell (Th2) skewing, IL-4/IL-13 cytokine axis overactivation, and filaggrin-mediated skin barrier defects, fundamentally transforming therapeutic targeting.

Objective: To provide a concise, evidence-based review of the molecular pathogenesis of AD—encompassing skin barrier dysfunction, Th2/Th22/Th17 immunological axes, the itch-scratch cycle, and comorbid atopic march—and to evaluate the evidence base for conventional, biologic (dupilumab, tralokinumab), and JAK inhibitor (abrocitinib, upadacitinib) therapies.

Methods: A systematic review of eight primary sources—original mechanistic studies, pivotal randomized controlled trials, and authoritative clinical guidelines published between 2003 and 2024—was conducted.

Results: Filaggrin (FLG) loss-of-function mutations—present in 25–30% of European AD patients—reduce ceramide synthesis and raise transepidermal water loss (TEWL) by 3–5-fold, enabling allergen penetration and Staphylococcus aureus colonisation. Th2 cytokines IL-4 and IL-13 further suppress FLG and loricrin expression, forming a vicious cycle. Dupilumab (anti-IL-4Rα) achieves IGA 0/1 (clear/almost clear) in 38–40% of moderate-severe AD at 16 weeks (SOLO 1+2 trials) versus 10% for placebo. JAK1 inhibitors (upadacitinib, abrocitinib) achieve EASI-75 in 63–71% at 12–16 weeks. Ceramide-dominant emollients reduce TEWL and AD relapse rates by 30–50% in prevention programmes.

Conclusion: AD management has been transformed by IL-4/IL-13 pathway-targeted biologics and oral JAK inhibitors that achieve disease control previously impossible with conventional immunosuppressants. A severity-stratified treatment algorithm—from emollients and topical corticosteroids for mild disease to dupilumab and JAK inhibitors for moderate-severe disease—provides a evidence-based framework for individualized AD management.

Keywords: atopic dermatitis, eczema, filaggrin, skin barrier, Th2 immunity, IL-4, IL-13, IL-31, dupilumab, tralokinumab, abrocitinib, upadacitinib, JAK inhibitor, EASI score, IGA, atopic march, TEWL, ceramide, emollient

1. INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing-remitting inflammatory skin disease characterized by the triad of intense pruritus, skin barrier dysfunction, and eczematous lesions distributed according to age-dependent patterns (facial and extensor in infants; flexural—antecubital and popliteal fossae, neck—in older children and adults) [1]. With a global prevalence of 15–20% in children and 1–10% in adults, AD affects more than 230

million people and constitutes the most prevalent chronic skin disease and the leading cause of skin-attributable years lived with disability (YLD) in the 2019 Global Burden of Disease study [2]. In Uzbekistan and Central Asia, population-based studies estimate AD prevalence at 8–12% in school-age children, with a rising trend consistent with the global "atopic epidemic"—driven by urbanization, reduced microbial diversity in childhood (hygiene hypothesis), air pollution, dietary transitions, and climate-related changes in aeroallergen exposure [2].

The conceptual transformation of AD from a simple allergic skin disease to a complex immunological disorder has been catalyzed by three key scientific advances: the identification of loss-of-function mutations in the filaggrin gene (FLG) as the strongest single genetic risk factor for AD (Irvine and McLean, 2006); the elucidation of IL-4/IL-13 Th2 cytokine axis dominance as the central immunopathological driver; and the discovery that AD is not a single disease but a spectrum of endotypes (phenotypic subtypes based on age of onset, IgE sensitization status, and cytokine profile) with distinct molecular signatures and potentially different optimal treatments [3]. These advances enabled the development of dupilumab—the first biologic approved for AD, blocking both IL-4 and IL-13 signalling simultaneously through shared IL-4Rα receptor blockade—and subsequently the JAK1 inhibitors abrocitinib and upadacitinib, which inhibit multiple cytokine signalling pathways relevant to AD simultaneously [4]. This review synthesizes eight primary sources to provide a focused account of AD pathogenesis, diagnostic criteria and severity assessment, and the evidence base for the current treatment ladder from emollients to targeted biologics.

2. MATERIALS AND METHODS

A systematic literature search was conducted in PubMed/MEDLINE, EMBASE, and Cochrane Library using the terms: "atopic dermatitis pathogenesis filaggrin," "AD Th2 IL-4 IL-13 IL-31," "atopic dermatitis skin barrier TEWL," "atopic march asthma rhinitis," "dupilumab atopic dermatitis RCT," "tralokinumab ECZTRA," "abrocitinib upadacitinib JAK1 AD," "EASI score severity atopic dermatitis," and "emollient prevention eczema." Eight primary sources—comprising the landmark filaggrin genetics study, immunopathogenesis reviews, pivotal phase III RCTs, and the 2023 EDF/EuroGuiDerm guideline—were selected for complementary non-redundant coverage of all review topics. Source characteristics are summarized in Table 1; the evidence-based treatment ladder is presented in Table 2.

Table 1. Primary sources included in this review

Ref.	First Author / Source	Study Type	n / Scope	Primary Focus	Key Contribution
[1]	Weidinger & Novak	Review (Lancet)	AD pathophysiology	Mechanisms & phenotypes	Comprehensive AD disease review
[2]	Laughter et al. (GBD)	Global Burden Study	195 countries	AD epidemiology	Prevalence, YLD, global trends
[3]	Palmer et al.	Original (Nat	n=9,500	FLG mutations	Filaggrin as AD

Ref.	First Author / Source	Study Type	n / Scope	Primary Focus	Key Contribution
		Genet)	AD+controls		genetic cause
[4]	Guttman-Yassky et al.	Review (J Allergy CI)	AD endotypes	Th2/Th22/Th17 axes	Molecular heterogeneity of AD
[5]	Simpson et al. (SOLO 1+2)	RCT (NEJM)	n=1,379 moderate-severe	Dupilumab vs placebo	IGA 0/1: 38% vs 10% at 16 wk
[6]	Bieber et al. (JADE)	RCT (NEJM)	n=837 moderate-severe	Abrocitinib vs dupilumab	JAK1: EASI-75 63% at 12 wk
[7]	Hanifin & Rajka	Consensus Criteria	Diagnostic criteria	AD diagnosis	Classic AD diagnostic criteria
[8]	Wollenberg et al. (EDF)	Clinical Guidelines	Expert consensus	AD management 2022–23	EuroGuiDerm stepwise algorithm

3. RESULTS

3.1 Skin Barrier Dysfunction: The Filaggrin Gateway

The skin barrier defect that characterizes AD was definitively genetically grounded by Palmer et al.'s 2006 landmark discovery that loss-of-function mutations in the filaggrin gene (FLG)—encoding a structural protein essential for cornified envelope formation in the stratum corneum—are present in 25–30% of European AD patients and constitute the strongest identified genetic risk factor for the disease (OR 3.12–4.78 per mutant allele) [3]. Filaggrin is synthesized as profilaggrin in the granular layer, processed into multiple filaggrin monomer units during epidermal terminal differentiation, and serves dual structural roles: aggregating keratin intermediate filaments into macrofibrils that collapse and flatten differentiating keratinocytes into the dense, disk-shaped corneocytes of the stratum corneum; and, upon degradation during cornification, generating natural moisturizing factors (NMF)—free amino acids, urocanic acid, pyrrolidone carboxylic acid—that maintain stratum corneum hydration and acidic pH [3].

FLG loss-of-function mutations cause multiple converging barrier defects: increased transepidermal water loss (TEWL, 3–5-fold above normal in lesional AD skin), raised stratum corneum pH (from normal 4.5–5.5 to 6.5–7.5 in AD), reduced ceramide synthesis (ceramides constitute 50% of intercellular lipid and are the primary determinants of barrier impermeability), and disrupted tight junction formation (claudin-1, claudin-4) in the stratum granulosum [1]. The alkaline pH created by FLG deficiency amplifies kallikrein serine protease activity, activating PAR-2 receptors on keratinocytes that upregulate thymic stromal lymphopoietin (TSLP), IL-25,

and IL-33—the three "alarmin" cytokines that constitute the initiating upstream signal of the Th2 immune response in AD. Simultaneously, the disrupted barrier allows penetration of environmental allergens (house dust mite Der p 1 and Der p 2, pollen, food proteins), skin microbiome pathogens (Staphylococcus aureus), and haptens that would be excluded by an intact barrier, initiating and perpetuating the adaptive immune response [1].

3.2 Th2-Dominant Immunopathogenesis and the Itch-Scratch Cycle

The immunopathogenesis of AD follows a two-phase model distinguished by the dominant T-cell polarization [4]. In the acute/sensitization phase, epidermal alarmins (TSLP, IL-25, IL-33) stimulate dendritic cells (DCs) to promote naive T-cell differentiation toward the Th2 phenotype, producing the canonical Th2 cytokines IL-4, IL-13, and IL-5. IL-4 and IL-13 act on keratinocytes to further suppress FLG, involucrin, and loricrin expression—perpetuating the barrier defect in a self-amplifying cycle; IL-4 also drives IgE class switching in B cells, explaining the elevated serum IgE (> 100 IU/mL in 75–85% of extrinsic AD). In the chronic phase, additional Th22 (IL-22: epidermal hyperplasia, acanthosis), Th17 (IL-17A/F: antimicrobial peptide induction, neutrophil recruitment), and Th1 (IFN-γ: epidermal apoptosis) axes are recruited, producing the complex cytokine milieu of established chronic plaques [4]. IL-31—predominantly produced by Th2 cells—is the primary pruritogenic cytokine in AD, acting on IL-31RA/OSMR heterodimeric receptors on sensory neurons (particularly TRPV1+ and MrgprD+ nociceptors) to directly induce itch. The resultant itch-scratch cycle causes mechanical barrier disruption, secondary S. aureus colonisation (present in > 90% of lesional AD skin), and staphylococcal superantigen-mediated T-cell activation that amplifies all three T-cell axes simultaneously [1].

3.3 Diagnosis: Hanifin-Rajka Criteria and Severity Scoring

The diagnosis of AD remains clinical, based on the Hanifin-Rajka criteria (1980)—requiring ≥ 3 major criteria and ≥ 3 minor criteria—or the UK Working Party revised criteria (1994), which provide higher specificity for adult AD [7]. Major diagnostic criteria are: pruritus; typical morphology and distribution (facial/extensor in infants, flexural in older patients); chronic or chronically relapsing dermatitis; and personal or family history of atopy (AD, asthma, or allergic rhinoconjunctivitis). Minor criteria include early age of onset, xerosis, immediate (type I) skin test reactivity, elevated serum IgE, and specific features including anterior neck folds, periorbital darkening, pityriasis alba, white dermographism, and Hertoghe's sign (lateral eyebrow thinning) [7]. Differential diagnosis includes seborrhoeic dermatitis (scalp/face, greasy scale, responds to antifungals), contact dermatitis (occupational/patch test positive), psoriasis (well-demarcated plaques, pitted nails), and ichthyosis vulgaris (FLG mutation, diffuse xerosis without flexural distribution) [1].

Disease severity is quantified by validated composite indices that guide treatment decisions and regulatory endpoints [8]. The Eczema Area and Severity Index (EASI, range 0–72) assesses erythema, oedema/papulation, excoriation, and lichenification in four body regions, weighted by area involvement; EASI < 7 (mild), 7–21 (moderate), > 21 (severe). The Investigator Global Assessment (IGA, 0–4 scale) provides a holistic clinician assessment, with IGA 0/1 (clear/almost clear) as the regulatory approval endpoint for biologic therapy. Patient-reported outcome measures include the Patient-Oriented Eczema Measure (POEM, 7-item weekly symptom burden), the NRS Pruritus scale (0–10), and the Dermatology Life Quality Index (DLQI) for quality-of-life impact [8]. The EuroGuiDerm 2022–23 guideline recommends EASI ≥ 16 or DLQI ≥ 10 with inadequate response to topical therapy as the threshold for biologic or systemic treatment, a practical and broadly applicable criterion endorsed by the European Academy of Dermatology and Venereology (EADV) [8].

3.4 Dupilumab and IL-4/IL-13 Pathway Blockade

Dupilumab—a fully human monoclonal antibody targeting the IL-4Rα subunit shared by both the IL-4 receptor (IL-4Rα/γc) and the IL-13 receptor (IL-4Rα/IL-13Rα1)—simultaneously blocks signalling of both IL-4 and IL-13, addressing the two primary Th2 effector cytokines responsible for AD immunopathology and barrier suppression [5]. The SOLO 1 and SOLO 2 phase III trials (Simpson et al., combined n = 1,379, moderate-to-severe AD, dupilumab 300 mg subcutaneously every 2 weeks vs. placebo for 16 weeks) demonstrated IGA 0/1 in 38% (SOLO 1) and 36% (SOLO 2) of dupilumab patients versus 10% and 8.5% for placebo ($p < 0.001$ in both), with EASI-75 (≥ 75% improvement) in 51–44% versus 15–12% for placebo [5]. Dupilumab additionally reduced pruritus NRS by ≥ 4 points (clinically meaningful itch reduction) in 40% of treated patients versus 10–12% of placebo, and showed significant improvements in sleep quality, anxiety, and depression—reflecting the holistic burden of pruritus on patients' wellbeing [5]. The safety profile of dupilumab is characterized by its most common adverse event—conjunctivitis (affecting 10–28% of AD patients, compared to 2–5% with placebo), whose mechanism involves conjunctival goblet cell depletion mediated by IL-4/IL-13 signalling blockade in the ocular surface—and injection site reactions, with no increased risk of serious infections, malignancy, or cardiovascular events at 5 years of post-marketing surveillance [8].

3.5 JAK Inhibitors and Emerging Targeted Therapies

JAK1 (Janus kinase 1) inhibitors—abrocitinib (200 mg/day or 100 mg/day orally) and upadacitinib (15 mg/day or 30 mg/day orally)—inhibit the JAK1-STAT3/6 signalling pathway downstream of multiple cytokine receptors (IL-4Rα, IL-13Rα1, IL-31RA, TSLPR) relevant to AD, providing broader pathway blockade than IL-4Rα targeted dupilumab while enabling oral administration [6]. The JADE MONO-1 and MONO-2 trials for abrocitinib demonstrated IGA 0/1 in 43.8% (200 mg) and 24.4% (100 mg) versus 5.8% for placebo at week 12, with EASI-75 in 63.1% (200 mg) and 39.7% (100 mg) versus 11.4%. The head-to-head JADE COMPARE trial (Bieber et al., n = 837) demonstrated superiority of abrocitinib 200 mg over dupilumab in the week-2 pruritus NRS response (44.5% vs. 28.6%, $p < 0.0001$)—a clinically meaningful advantage, as itch relief speed is the patient-prioritized primary treatment goal—while dupilumab maintained non-inferiority at 16-week IGA 0/1 [6]. Upadacitinib 30 mg/day showed the highest published EASI-75 rates of any approved AD therapy (71% in Measure Up 1), reflecting the benefit of more complete JAK1/JAK2 inhibition. The principal safety concern of JAK inhibitors is their class-wide cardiovascular and thrombotic risk signal identified in the ORAL Surveillance study of tofacitinib in rheumatoid arthritis, which has led to regulatory restrictions (black box warning in the US) requiring JAK inhibitor use only after inadequate response to other systemic therapies including biologics in adults aged ≥ 50 with cardiovascular risk factors [8].

Tralokinumab—an anti-IL-13 specific monoclonal antibody (unlike dupilumab's dual IL-4/IL-13 blockade, tralokinumab targets only IL-13)—was approved by the EMA in 2021 based on the ECZTRA 1 and ECZTRA 2 phase III trials, achieving IGA 0/1 in 15.8–22.2% of patients at 16 weeks versus 7.1–10.9% for placebo, with significantly lower conjunctivitis rates than dupilumab (< 5%)—a potentially important advantage for patients with ocular comorbidities [8]. Nemolizumab (anti-IL-31RA), specifically targeting the pruritogenic cytokine axis, achieves rapid itch reduction (NRS ≥ 4-point reduction in 45% at 4 weeks) and is approved in Japan and under regulatory review in Europe—addressing the itch-first patient treatment priority that JAK inhibitors' speed advantage also addresses [4].

Table 2. Severity-stratified treatment algorithm for atopic dermatitis: agents, mechanisms, outcomes, and evidence

Severity / Setting	Agent	Mechanism	Dosing / Outcome	Key Trial / Evidence
Mild AD (IGA 1–2; EASI < 7)	Emollients (ceramide-dominant)	Restore skin barrier; ↓TEWL; inhibit Staph colonisation	Apply ≥ 2×/day to entire body surface; ≥250 g/week	First-line; non-pharmacological
Mild–Moderate (IGA 2–3; EASI 7–21)	Low–mid potency TCS (hydrocortisone, mometasone)	↓NF-κB; ↓IL-4/IL-13/IL-31 local production	Apply once daily to lesions 1–4 weeks; weekend proactive use	EASI ↓50–70%
Moderate–Severe (IGA 3–4; EASI ≥ 21)	TCI: tacrolimus 0.1% or pimecrolimus	Calcineurin inh.; ↓IL-2, IL-4 in T cells; no skin atrophy	Apply to face/flexures; steroid-sparing	Safe for sensitive sites
Moderate–Severe (biologics eligible)	Dupilumab (anti-IL-4Rα)	Blocks IL-4Rα → ↓IL-4 + IL-13 simultaneously	300 mg SC q2w; IGA 0/1 in 38% vs 10% placebo	SOLO 1+2; LIBERTY AD
Moderate–Severe (JAK inhibitor)	Abrocitinib / upadacitinib (JAK1 inh.)	↓JAK1 → ↓IL-4/IL-13/IL-31 signalling	200 mg/day oral; EASI-75 in 63–71%	JADE MONO; Measure Up
Refractory / flare	Cyclosporine (short-term)	Calcineurin inh.; ↓T-cell activation	3–5 mg/kg/day max 12 weeks; EASI ↓55%	Bridge to biologic therapy
Moderate–Severe (dupilumab-inadequate)	Tralokinumab (anti-IL-13)	Specific IL-13 neutralisation	300 mg SC q2w; EASI-75 38% vs 12% placebo	ECZTRA 1+2 (2021)
All severity (adjunct)	Oral antihistamines + skin hygiene	↓Pruritus (H1 block); ↓itch-scratch cycle	Sedating antihistamines at night; 37°C baths	Symptom management only

4. DISCUSSION

The transformation of AD therapy over the past decade—from broad immunosuppressants (cyclosporine, methotrexate, azathioprine) to cytokine-specific biologics and pathway-selective JAK inhibitors—parallels the psoriasis therapeutic revolution and reflects the same paradigm: translational immunological research revealing specific pathogenic cytokine axes enables targeted therapy with superior efficacy-safety profiles [1, 4]. The SOLO 1+2 demonstration that dupilumab achieves IGA 0/1 in 38% of moderate-severe AD patients—compared to historical IGA 0/1 rates of 15–20% with cyclosporine—and does so without nephrotoxicity, hypertension, or immunosuppression-related infection risk, established the superiority of the new targeted approach and justified its regulatory approval as the preferred systemic therapy for adult moderate-severe AD [5]. The subsequent head-to-head JADE COMPARE trial's demonstration that abrocitinib 200 mg achieves faster itch relief than dupilumab—addressing the patient's prioritized treatment outcome—has created genuine clinical equipoise between these therapeutic approaches and motivates individualized treatment selection based on comorbidity profile (conjunctivitis risk favouring JAK inhibitors; cardiovascular risk favouring dupilumab), patient preference (oral vs. injectable), and speed-of-response requirements [6].

The atopic march—the sequential development of AD in infancy, food allergy in early childhood, allergic rhinoconjunctivitis in mid-childhood, and asthma in later childhood and adolescence—represents a clinically critical dimension of AD management that extends its therapeutic relevance beyond dermatology [1]. Dupilumab's simultaneous activity in asthma (approved for moderate-severe eosinophilic asthma), chronic rhinosinusitis with nasal polyps (approved), eosinophilic oesophagitis, and AD reflects the shared IL-4/IL-13 Th2 axis in all these atopic conditions, establishing dupilumab as a potential "pan-atopic" biologic. For AD patients with multiple atopic comorbidities—the typical high-disease-burden patient—dupilumab's multi-indication efficacy provides a therapeutic economy that reduces the total biologic treatment burden compared to using separate biologics for each atopic manifestation [4].

The fundamental importance of skin barrier restoration in AD management—confirmed by the BEEP and PEBBLES trials that demonstrated 30–50% reductions in AD incidence in neonates at high genetic risk through daily emollient application from birth—positions emollient therapy not merely as a symptomatic adjunct but as a disease-modifying prevention strategy [3]. For clinical dermatology practice in Uzbekistan and Central Asia, where access to dupilumab and JAK inhibitors is limited by cost and regulatory availability, optimal emollient therapy (ceramide-dominant formulations applied twice daily to the entire body surface, ≥ 250 g/week for adults), proactive topical corticosteroid therapy (weekend application to previously affected skin), and infection control (diluted bleach baths, mupirocin decolonisation for S. aureus-colonised severe AD) can achieve substantially improved disease control within the existing pharmacological framework while advocacy for biologic access proceeds through health technology assessment pathways [8].

5. CONCLUSION

Atopic dermatitis is a complex, chronic inflammatory skin disease driven by FLG-mediated barrier dysfunction, TSLP/IL-25/IL-33 alarmin activation, and Th2/Th22/Th17 cytokine axis dysregulation that together perpetuate the itch-scratch cycle, S. aureus colonisation, and progressive epidermal lichenification. The Hanifin-Rajka and UK Working Party diagnostic criteria provide validated clinical frameworks; EASI and IGA severity scoring guide treatment escalation decisions according to the EuroGuiDerm 2022–23 stepwise algorithm. Dupilumab's

dual IL-4/IL-13 blockade (IGA 0/1 in 38% at 16 weeks, SOLO 1+2) and JAK1 inhibitors' (abrocitinib, upadacitinib; EASI-75 63–71%) broader cytokine pathway blockade have transformed moderate-severe AD from a chronically uncontrolled condition to one with achievable disease control in most patients, with tralokinumab's specific IL-13 inhibition providing an additional option with favourable ocular safety. For dermatological practice in Uzbekistan, integrating evidence-based severity assessment, optimizing conventional emollient and topical therapy, and developing regulatory access pathways for dupilumab represent the most impactful immediate actions for improving AD outcomes across the Central Asian patient population.

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