Pathogenesis of Atopic Dermatitis and Treatment Targets

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David E Cohen has declared the following financial interests:

Consultant and Honorarium:
- Ferndale Laboratories,
- Asana
- Medimetriks,
- Cutanea,
- Ferrer,
- Celgene,
- Dermavant
- FSJ
- FIDE. (FIDE receives industry sponsorship from AbbVie, Almirall, Amgen, Bausch and Lomb, Bristol-Myers Squibb, Celgene Dermavant, Dermira, Janssen, Kyowa Hakko Kirin, LEO, Lilly, Novartis, Ortho Dermatologics, Pfizer, Sanofi Genzyme, Sun Pharma, UCB, Valeant)

Stock or stock options: Dermira, Medimetriks, Brickell Biotech, Kadmon

Board of Directors: Dermira, Kadmon
Atopic Dermatitis - co-factors

Purported influencing factors
- prenatal exposures
- Irritants
- pruritogens
- pathogens
- climate factors
- temperature
- humidity
- ultraviolet radiation
- outdoor and indoor air pollutants
- tobacco smoke exposure,
- water hardness
- urban vs. rural living
- diet
- breastfeeding
- probiotics and prebiotics

Adult AD cohort had a significantly higher prevalence of:
- nasal allergies (46.4% vs. 19.8%)
- asthma (22.4% vs. 7.9%),
- neuropsychiatric conditions such as anxiety (42.5% vs. 21.3%)
- depression (37.2% vs. 20.9%) (all P < 0.0001).
- Higher resource use (healthcare practitioner visits, emergency room, hospitalizations) (P < 0.05)

A global epidemiology survey of the prevalence and severity of AD: All patients

All ages (0–18+)
- 0–4%
- 5–8%
- 9–12%
- 13–16%

Canada: 9%
USA: 9%
Mexico: 12%
USA: 9%
Brazil: 11%
France: 7%
Spain: 11%
UK: 10%
Germany: 6%
Italy: 8%
Switzerland: 5%
Turkey: 12%
China: 14%
South Korea: 14%
Japan: 6%
Saudi Arabia: 10%
Taiwan: 9%
Japan: 6%
Australia: 10%

Silverberg J, et al. EADV 2018, FC01.01. Sponsored by Pfizer
Cross-sectional, web-based, international survey: Epidemiology of AD in adults

### Prevalence of adult AD

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>Self-report of physician-diagnosed AD</th>
<th>Point prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>9897</td>
<td>16.7%</td>
<td>8.1% (7.5–7.7%)</td>
</tr>
<tr>
<td>Spain</td>
<td>9924</td>
<td>11.1%</td>
<td>7.2% (6.7–7.7%)</td>
</tr>
<tr>
<td>US</td>
<td>19,986</td>
<td>11.9%</td>
<td>4.9% (4.6–5.2%)</td>
</tr>
<tr>
<td>EU</td>
<td>49,757</td>
<td>9.4%</td>
<td>4.4% (4.2–4.6%)</td>
</tr>
<tr>
<td>France</td>
<td>9964</td>
<td>9.0%</td>
<td>3.6% (3.2–4.0%)</td>
</tr>
<tr>
<td>Canada</td>
<td>10,004</td>
<td>8.1%</td>
<td>3.5% (3.1–3.9%)</td>
</tr>
<tr>
<td>UK</td>
<td>10,001</td>
<td>6.7%</td>
<td>2.5% (2.2–2.8%)</td>
</tr>
<tr>
<td>Germany</td>
<td>9971</td>
<td>5.4%</td>
<td>2.2% (1.9–2.5%)</td>
</tr>
<tr>
<td>Japan</td>
<td>10,011</td>
<td>4.3%</td>
<td>2.1% (1.8–2.3%)</td>
</tr>
</tbody>
</table>

- Superscript letters show significantly higher point prevalence than the indicated countries (P<0.05)

Barbarot S, et al. EADV SEPT 2017, OP04.05 Sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.
A study of 1678 patients with AD in routine care: Patient needs, predictors of quality of life, and association with clinical outcomes

• **Objective:** Determine QoL predictors and needs in German AD patients (Augustin)

• Clinical sample from 174 randomly selected clinics in Germany: HR criteria for AD diagnosis, DLQI and other variables

**Comparison of QoL in patients with AD and psoriasis (n=1678)**

<table>
<thead>
<tr>
<th>DLQI (0=minimum, 30=maximum)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>12%</td>
</tr>
<tr>
<td>2–5</td>
<td>30%</td>
</tr>
<tr>
<td>6–10</td>
<td>20%</td>
</tr>
<tr>
<td>11–20</td>
<td>15%</td>
</tr>
<tr>
<td>21–30</td>
<td>5%</td>
</tr>
</tbody>
</table>

- **Atopic dermatitis** (mean 8.5)
- **Psoriasis** (mean 7.5)

**Generic QoL (EQ-5D) (n=1678)**

- Population average

**Mean VAS**

- **AD**
  - 18–24: (n=263)
  - 25–34: (n=549)
  - 35–44: (n=837)
  - 45–54: (n=637)
  - 55–64: (n=597)
  - 65–74: (n=416)
  - 75+: (n=247)

Augustin M, et al. EADV 2018, FC01.08
Hannifin Criteria: Major criteria (need 3 or more) are as follows:

- Pruritus
- Typical morphology and distribution
- Flexural lichenification in adults
- Facial and extensor involvement in infants and children
- Dermatitis - Chronically or chronically relapsing
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Hanifin - Minor criteria (need 3 or more) are as follows:

- Cataracts
- Cheilitis
- Conjunctivitis - Recurrent
- Eczema - Perifollicular accentuation
- Facial pallor or erythema
- Food intolerance
- Hand dermatitis - Nonallergic
- Ichthyosis
- IgE - Elevated
- Immediate (type I) skin test reactivity
- Infections (cutaneous)
- Dennie-Morgan infraorbital fold
- Itching when sweating
- Keratoconus
- Keratosis pilaris
- Nipple dermatitis
- Orbital darkening
- Palmar hyperlinearity
- Pityriasis alba
- White dermographism
- Wool intolerance
- Xerosis

Guidelines of care for the management of atopic dermatitis

Section 1. Diagnosis and assessment of atopic dermatitis

Box 1. Features to be considered in the diagnosis of patients with atopic dermatitis:

**ESSENTIAL FEATURES**—Must be present:
- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

*Patterns include:

1. Facial, neck, and extensor involvement in infants and children
2. Current or previous flexural lesions in any age group
3. Sparing of the groin and axillary regions

**IMPORTANT FEATURES**—Seen in most cases, adding support to the diagnosis:
- Early age of onset
- Atopy
  - Personal and/or family history
  - Immunoglobulin E reactivity
- Xerosis

**ASSOCIATED FEATURES**—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:
- Atypical vascular responses (e.g., facial pallor, white demographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (e.g., perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

**EXCLUSIONARY CONDITIONS:** It should be noted that a diagnosis of AD depends on excluding conditions such as:
- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Two Major Hypotheses on Development of Inflammation

Outside-Inside View

1. Primary defect in epithelial barrier
2. Secondary immunologic dysregulation
3. Inflammation

Inside-Outside View

1. Primary immune dysfunction
2. IgE sensitization and secondary epithelial-barrier disturbance
Pathogenesis of Atopic Dermatitis: Associated **Structural and Functional** Changes

- Filaggrin (FLG) loss-of-function variants (null-alleles) are associated with eczema and asthma in association with eczema.

- Aberrant expression of cathelicidins and altered host defenses. (innate immunity)

- A deficiency of ceramides in the stratum corneum is an essential etiologic factor for the dry and barrier-disrupted skin of patients with atopic dermatitis (AD) and increased TEWL.

J Cell Sci. 2009 May 1;122(Pt 9):1285-94.
Histology of normal vs. AD skin

Natural Moisturizing Factor (NMF)

• Filaggrin is a vital protein required for SC formation and hydration
  – It acts as a source of hygroscopic amino acids and their derivatives, known as natural moisturizing factor (NMF)

• Along with SC lipids, NMF is one of the most significant influences on water flux and retention in the skin
Ceramides/Lipids play a crucial role in barrier function

- Ceramides are the most common constituent among SC lipids, accounting for up to 50% of total intercellular lipids
- Ceramide 1 and 3 levels are significantly reduced and the quantity of ceramide 3 were significantly correlated with TEWL impairment in AD subjects
- Type 2 allergy alters skin lipid metabolism

![Chemical structure of ceramides]

AD: Increased susceptibility to infections

- Aberrant expression of Cathelicidins and altered host defenses. (innate immunity)
  - Viral
    - Molluscum contagiosum, HSV, Smallpox
  - Fungal infections
    - Tinea, *Malassezia*
  - Bacterial
    - *Staphylococcus aureus*
      - Colonization $\leftrightarrow$ Infection
Pattern Recognition Receptor (PRR)

- Recognize pathogens but distinguish it from the host
Quandary of Atopic Inflammation - The inflammatory component drives the structural abnormalities.

- The **Th2 cytokines** IL-4 and IL-13, (Th2) can lower Filaggrin protein expression
- Similarly, **IL-4 and IL-13 can enhance the expression and function of the serine protease kallikrein 7** of human keratinocytes in vitro
  - Increases degradation of corneodesmosome proteins and promotes desquamation.
- **AMP production in AD is in part impeded by the Th2-dominated inflammation.**
- Elevated IgE in extrinsic AD is confounding.

Atopic Dermatitis is largely driven by the Th2 pathway [lebrikizumab and tralokinumab], Th22, Th1 and Th17, IL-24 pathways, epidermal barrier dysfunction, itching [nemolizumab], and JAK/STAT signaling [baricitinib, upadacitinib, abrocitinib, ASN002, tofacitinib, ruxolitinib, and delgocitinib], IL-5, and other intracellular processes (PDE and tapinaroff).

**ADVERSE REACTIONS**

*Atopic Dermatitis:* Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)
• Ligands cause the receptors to dimerize, and the JAKs then phosphorylate each other.
• STATs then bind to the phosphorylated JAK and they get tyrosine-phosphorylated by the activated JAKs.
• STATs then dissociate from the JAKs and move to the nucleus to influence cellular function.
JAK and TYK2 mediate signaling of cytokines

TYK2 signaling pathways

JAK signaling pathways

<table>
<thead>
<tr>
<th>JAK1 Blockade</th>
<th>JAK1/2 Blockade</th>
<th>JAK1/2/3 Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>IL-4</td>
<td>IL-2</td>
</tr>
<tr>
<td>IL-13</td>
<td>IL-13</td>
<td>IL-4</td>
</tr>
<tr>
<td>IL-22</td>
<td>IL-22</td>
<td>IL-7</td>
</tr>
<tr>
<td>IFN a/g</td>
<td>IFN a/g</td>
<td>IL-15</td>
</tr>
<tr>
<td>IL-15</td>
<td>IL-15</td>
<td>IL-15</td>
</tr>
</tbody>
</table>

Most commercial products have black boxed warnings for:
- Infections and TB
- Malignancy
- Blood monitoring
- Thrombosis and thromboembolic events
**cAMP** are important second messengers from extracellular stimuli and PDE regulates the intracellular concentration of cAMP

![Diagram of cAMP signaling pathway](image)

**cAMP** - blocks the production of pro-inflammatory cytokines (interferon-γ, tumor necrosis factor-α, interleukin [IL]-4, 12, IL-17, and IL-23. Increases IL-10

**Warnings and precautions**
- Diarrhea, Nausea, Vomiting
- Depression
- Weight loss
- Drug interactions
Summary of AD:

• As our understanding of the pathophysiology of AD gets further elucidated, the capacity to target new mechanisms improves.

• Newer therapies offer the opportunity for more targeted approaches with potentially fewer adverse events.
Thank you

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