Atopic Dermatitis

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Overview

• 1. Genes and pathogenesis
• 2. Natural history and disease course
• 3. Comorbidities
• 4. Treatments
• 5. Prevention

Barrier Defects

- One of the primary drivers that leads or aggravates polarized immune dysfunction
- Filaggrin is an epidermal protein involved in normal differentiation and optimal function of the stratum corneum
- Defects in filaggrin result in a phenotype associated with asthma as well as contact dermatitis, peanut allergy

Filaggrin

- Early-onset atopic dermatitis with a propensity toward asthma
- 30% of European patients with AD have mutations in FLG identified
- 40% of all carriers of FLG-null alleles never have any signs of eczema

Other genes

- HyperIgE
  - STAT3, DOCK8, TYK2
- Eczematous dermatitis with atopy
  - SPINK5
- Other genes: FLG2, serum corneum chymotryptic enzyme, COL29A1, TSLP

Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis

Polygenic disease

- Genes
  - Barrier function: FLG, COL29A1, FLG2

Polygenic Disease

- Genes
  - Barrier function: FLG, COL29A1, FLG2
  - Immune function, TH2, TSLP, TH17

Atopic Subtypes and Functional Endotypes

- Extrinsic v intrinsic
- Early-onset and later-onset
- European and non-European
- FLG and non-FLG
Age-Related Changes in the Microbiome of AD Patients

Treatment-Related Changes in the AD Microbiome

AD-Associated Microbiome

- Pediatric and adult microbiomes are different
- Treatment of AD skin with anti-inflammatory agents and with bleach baths reduces relative populations of staphylococci and increases diversity and microbiome richness

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Persistence

• Spontaneous remission in up to 70% by adolescence
  Bieber. NEJM. 2008;358:1483-94.

Persistence

• Cross-sectional cohort study of the PEER database
  – 7157 subjects for 22,550 person-years
  – At least 2 years of follow-up: 4248
  – At least 5 years of follow-up: 2416
  – At every age from 2-26 yo, more than 80% had symptoms or were using AD medication
  – >50% of those with >6 months symptom-free: age 20 yo

Persitence

Comorbidities

• Cardiovascular risks
  – Obesity
  – Systolic BP
  – Coronary artery calcification, myocardial infarction, congestive heart disease, angina, stroke, peripheral vascular disease
• Behavioral disorders and neuropsychiatric issues
  – Depression, anxiety, suicidal ideation, ADHD, autism spectrum disorder
• Malignancy risks
  – Lymphoma, skin cancers

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Topical crisaborole ointment, 2%

• Small molecule PDE4 inhibitor
• PDE4 inhibition increases cAMP and inhibits transcription of proinflammatory cytokines associated with atopic dermatitis, including but not limited to NFAT and NFκB
• Rapid absorption, and inactivation into inactive metabolites, with steady state achieved within 3-6 days

Phase 3: Children & Adults with Mild to Moderate AD
- Multicenter, double-blind, vehicle-controlled
- Phase 3 studies
  - BID application to all treatable areas for 4 weeks
  - Primary efficacy endpoint: % achieving clear or almost clear ISGA with ≥2-grade improvement from baseline

Pruritus Scores

Apremilast
- Systemic small molecule PDE4 inhibitor
- Current indication: moderate-severe psoriatic arthritis
- Small open-label pilot study for AD in adults demonstrated safety and efficacy

Figure 2. Mean Eczema Area and Severity Index (EASI) scores per cohort at different time points with error bars representing standard deviations.

Figure 3. Mean visual analog scale (VAS) scores for pruritus at different time points with error bars representing standard deviations.
Apremilast

- Small open-label pilot study for AD in adults
  - 50% reduction in EASI
  - Main AE: nausea
  

- Phase 2 study in 10 subjects with recalcitrant moderate to severe AD or ACD
  - ≥2 point improvement in IGA in 20% at week 12
  

Ustekinumab

- IL-12/IL-23p40 antagonist
- Phase 2 randomized, double-blind, placebo-controlled, crossover study design
  - 33 patients with moderate-to-severe AD received drug as SQ injections or placebo at intervals of 0, 4, and 16 wks, and underwent crossover at 16, 20, and 32 wks
    - No severe drug-related AEs
    - Active drug group with superior SCORAD at 12, 16, and 20 wks compared with placebo, but not statistically significant
    - Possible confounding by design where patients continued to receive topical glucocorticosteroids and possible suboptimal dosing for AD
  

Ustekinumab for AD


Table I. Patient characteristics

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<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Age, y</td>
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<td>55</td>
<td>46</td>
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<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<tr>
<td>Onset of AD</td>
<td>Infancy</td>
<td>Infancy</td>
<td>Infancy</td>
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<tr>
<td>Family history for atopy</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>IgE levels</td>
<td>KU/L</td>
<td>&gt;5000</td>
<td>&gt;5000</td>
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<td>Allergic rhinitis</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Childhood asthma</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Asthma currently active</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Filagrin mutation</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Previous therapies</td>
<td>Oral corticosteroids</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td>PLEXA</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td></td>
<td>Narrowband UVB</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td>Cyclosporin A</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td></td>
<td>MTX</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Topical therapy</td>
<td>TCS T5</td>
<td>TCS T5</td>
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</table>

Dupilumab

- IL-4 and IL-13 antagonist
- Fully human monoclonal antibody delivered as a subcutaneous injection
- 16-week Phase 3 trials: SOLO1 and SOLO2
- Randomization 1:1:1
  - Placebo
  - 600 mg loading dose, then 300 mg weekly
  - 600 mg loading dose, then 300 mg q 2 weekly
- Similar adverse effect profile between arms except for conjunctivitis and injection site reactions which were higher for active drug

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Early Emollient Use and AD

- 124 infants in the UK and US
- High-risk for AD: 1° family relative with AD
- Randomized to receive either no emollient or emollient use (oil, cream/gel, or ointment)
  - UK: Sunflower seed oil, Doublebase gel, liquid paraffin 50% in white soft paraffin
  - US: Sunflower seed oil, Cetaphil cream, Aquaphor Healing Ointment
- Emollients: started within 3 weeks up to 6 mo


Early Emollient Use and AD

• Cumulative incidence of AD
  – Emollient group had a 50% reduction (RR, 0.50; 95% CI, 0.28-0.9; p=0.017)

• Safe, simple, low-cost intervention for AD-at-risk infants
• Validation in larger studies; longer-term follow-up; optimal timing and types of emollients need to be evaluated


Early Emollient Intervention Studies

  – 32% fewer AD cases in those using moisturizer over 32 weeks

  – 50% fewer AD cases in those using moisturizer over 56 weeks

  – Lower TEWL and skin pH in emollient-treated atopic preschool kids

Early Signs of AD

• 1903 infants
• TEWL at birth (2d), 2 and 6 mos
• Presence or absence of AD at 6 and 12 mos
• At 6 mos: 18.7% with AD; by 12 mos: 15.53%
• Upper quartile TEWL at either 2 days or 2 months was predictive of AD at 6 and 12 months, respectively

Kelleher et al. JACI. 2015 Jan;Epub ahead of print.

Some Potential Predictors of AD

• Elevated blood eosinophils ≥5% at 4 weeks of age was predictive of early-onset AD at 7 months (p=0.007), 1 year (p=0.004), 2 years (p=0.007), 3 years (p=0.006)

• Lower levels of macrophage inflammatory protein-beta in cord blood indicate immature immune responses in infants and correlated with AD risk


• Lack of commensal staphylococcal bacteria during the first 6 months was associated with development of AD at 12 months


Cost Effectiveness of Prophylactic Moisturizing

<table>
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<tr>
<th>Moisturizer</th>
<th>Base</th>
<th>Average Cost/ Application ($)</th>
<th>Total Cost ($)</th>
<th>ESI (ES/C)</th>
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<tbody>
<tr>
<td>Vanicream 1% poly</td>
<td>0.13</td>
<td>0.64</td>
<td>1.90</td>
<td>0.32 (0.17-0.56)</td>
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<tr>
<td>Sunflower seed oil</td>
<td>0.15</td>
<td>0.18</td>
<td>18.25</td>
<td>0.15 (0.06-0.42)</td>
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<td>Corti Moisturizing Cream</td>
<td>0.79</td>
<td>0.35</td>
<td>41.69</td>
<td>0.35 (0.15-0.71)</td>
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<td>Aquaphor Baby Healing Ointment</td>
<td>0.58</td>
<td>0.65</td>
<td>56.58</td>
<td>0.58 (0.35-0.96)</td>
</tr>
<tr>
<td>Cetaphil Moisturizing Cream</td>
<td>1.00</td>
<td>0.12</td>
<td>18.41</td>
<td>0.12 (0.05-0.19)</td>
</tr>
<tr>
<td>Aveeno Eczema Therapy Moisturizing Cream</td>
<td>1.40</td>
<td>0.45</td>
<td>42.13</td>
<td>0.45 (0.30-0.60)</td>
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<tr>
<td>Vanicream 1% poly</td>
<td>2.96</td>
<td>0.66</td>
<td>171.26</td>
<td>0.56 (0.35-0.84)</td>
</tr>
</tbody>
</table>

Cost Effectiveness of Prophylactic Moisturizing

- 3.6 grams per daily application at birth
- 6.6 grams per daily application at 6 months
- Used for 6 months
- Expected relative risk reduction of 50%
- Petrolatum: $353/quality-adjusted-life-years
- Most expensive: $45,000/QALY – UK threshold for cost-effectiveness $38,000/QALY
- Unclear if delay of onset or disease-modifying


Thumb-sucking and Nail biting

- Dunedin Multidisciplinary Health and Development Study
- 1037 patient cohort
- 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years
- 31% thumb-suckers or nail biters


Thumb-sucking and Nail biting

- Any oral habit, risk of atopic sensitization (SPT) but not asthma or hay fever:
  - At age 13 yo
    - OR 0.67, 95% CI 0.48–0.92, P = .013
  - At age 32 yo
    - OR 0.61, 95% CI 0.46–0.81, P = .001

Summary

- Filagrin is one of several genes that are important to the pathogenesis of AD
- AD is a polygenic disorder and relevant genes may include those that affect barrier structure and immune function
- Several atopic subtypes or endotypes are emerging, some based on genotypes and some on other functional criteria
- Microbiome diversity decreases prior to AD flares, and increases as successful treatment initiated
- AD may persist for longer than expected, into young adulthood
- AD may be best considered as a systemic inflammatory disorder with extracutaneous comorbidities
- Novel treatments for AD include a focus on PDE4, IL4 and 13, as well as TH17-mediated inflammation
- Prevention is possible and identification of potential markers of risk and potential interventions are emerging