Atopic Dermatitis: Review and updates

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• Disclosures
  – Anacor – Advisory Board
  – Regeneron – Upcoming study site

Lecture Objectives

• Explain the pathogenesis of atopic dermatitis
• Discuss the current management of atopic dermatitis
• Understand future treatment options
Burden of Atopic Dermatitis

• Up to $3.8 billion/year US alone
• Sleep deprivation
• Psychological effects
• Quality of life
• Atopic march

Atopic dermatitis

• Incidence rising
  – 2009-2011 estimated to affect 12.5% of children
• Age of onset
  – Most common between 3-6 mos of age
  – 60% by the age of 1
  – 90% by the age of 5
  – Rare cases with first onset in adulthood

Atopic dermatitis

• Majority with resolution by adulthood
  – Variable reports regarding persistence, may be more persistent than previously thought
    • 6 mos period of symptom/treatment free not reported in 50% until 20 yo (PEER study)
  – Increased persistence in children with disease > 10 years, later onset, more severe disease

Margolis JS. JAMA Dermatol 2014;150:593-600.
PATHOGENESIS:
GENETIC BARRIER DEFECT
Stratum corneum / Cornified layer
Stratum granulosum / Granular layer
Stratum spinosum / Spinous layer
Stratum basale / Basal layer

Primary Barrier

Cornification “Bricks and Mortar”
Keratinocyte in Granular Layer
Keratohyalin granule (Bricks)
- Filaggrin
- Involucrin
- Loricrin
- Other proteins

Lamellar granule (Mortar)
- Ceramides
- Cholesterol
- Fatty acids
- Other lipids

Cornification “Bricks and Mortar”
Keratinocyte
“Mortar” Lipid envelope
“Bricks” Cornified envelope
Keratohyalin granule
- Filaggrin
- Involucrin
- Loricrin
- Other proteins
Lamellar granule
- Ceramides
- Cholesterol
- Fatty acids
- Other lipids
Filaggrin

- Structural role in cornified envelope
- Degraded into natural moisturizing factor (NMF)

Decreased Filaggrin

- Decreased structural integrity of cornified envelope
- Decreased NMF $\rightarrow$ corneocytes shrink

Profilaggrin Mutations

- FLG null mutation causes ichthyosis vulgaris
- FLG loss-of-function mutations predispose to several diseases
  - 3-4x risk of atopic dermatitis
  - 3x risk of asthma in setting of atopic dermatitis
  - 5x risk of peanut allergy
Profilaggrin Mutations

- 15-50% of atopic dermatitis patients have a FLG mutation
- Stronger association with severe disease
- Ethnic variation

Other Epidermal Barrier Proteins

- Corneodesmosome
- Tight junction (claudin)
- Loricrin
- Involucrin
- Late cornified envelope protein

Proteases

- Proteases break down corneodesmosomes
- Protease inhibitors control protease activity
Increased Protease Activity

- Results in
  - Breakdown of corneodesmosomes
  - Activation of protease-activated receptor 2 (PAR2)
    - Inhibits lamellar body secretion
    - Mediates pruritus
    - Initiates innate inflammatory response

Acid Mantle

- Normal skin has pH of 4-6.5
- Importance of acidic pH
  - Antimicrobial effects
  - Favors protease inhibitor activity > protease activity
  - Optimal for lipid-generating enzymes

Elevated pH

- ↓ filaggrin → ↓ NMF → ↑ pH
- AD patients have higher skin pH
  - Even in uninvolved skin
  - Higher pH during flare
PATHOGENESIS: ACQUIRED BARRIER DEFECTS AND ENVIRONMENTAL STIMULI

Soaps and Detergents
• Solubilizes lipids
• Promotes release of pro-inflammatory cytokines
• Increases pH of the skin

House Dust Mites
• Contain proteolytic enzymes
• Directly activate PAR2
  – Mediates pruritus
  – Initiates innate inflammatory response
  – Inhibits lamellar body secretion
**Staphylococcus aureus**

- AD patients frequently colonized
  - Lesional skin (70%, OR 19.74)
  - Non-lesional skin (39%, OR 7.77)
- Produce proteases
- Secrete enzymes that interfere with lipid lamellae
- Produce superantigens

_Totte et al, Br J Dermatol, 2016_

**Specific IgE Production**

- *Malassezia* species
- *S. aureus*
- *Candida albicans*
- *Aspergillus*
- Dust mites
- Environmental allergens

**PATHOGENESIS:**
**GENETIC IMMUNOLOGICAL PROFILE**
Pattern Recognition Receptors

• Recognize and bind pathogens
• Polymorphisms associated with atopic dermatitis
  – Toll-like receptor 2 (TLR2)
  – Nucleotide-binding oligomerization domain-containing protein 1 (NOD1)
  – CD14

Pattern Recognition Receptors

• Defects result in:
  – Susceptibility to infection
  – Promote TH2 inflammatory response

Antimicrobial Peptides (AMPs)

• Kill microbes and modulate immune response
• Decreased levels of AMPs in AD
  – e.g. cathelicidin and beta-defensin
• Human beta-defensin polymorphism associated with AD
Innate Immune Cells

- Decreased levels and functional defects of:
  - Natural killer cells
  - Plasmacytoid dendritic cells
  - Neutrophils
- Predispose to infections

Innate Immune Cells

- Increased levels of:
  - Eosinophils
  - Mast cells
  - Basophils
- Aggravate inflammatory response and compromise epidermal barrier

Thymic Stromal Lymphopoietin

- Released by keratinocytes
- Triggered by:
  - Mechanical stimulation
  - Allergens
  - Microbial pathogens
- TSLP polymorphisms → higher levels
T Cell Response

- Th2 response predominates in acute AD
  - IgE production
  - Decrease filaggrin and ceramide expression
  - Increased S. aureus binding and inhibited killing
  - Downregulate AMPs
  - Stimulates itch in sensory neurons (IL-31)
- Th1, Th17, and Th22 responses predominate in chronic AD
  - Promotes epidermal hyperplasia
  - Decrease filaggrin expression
Comorbidities

- Asthma
- Seasonal/food/environmental allergies
- Allergic rhinitis
- Many controversial emerging comorbidities...
  - Neuropsychiatric
  - Obesity
  - Cardiovascular

Diagnosis

- Clinical diagnosis
- Modified Hanifin and Rajka criteria
  - Essential features
    - Pruritus
    - Eczema
  - Typical and age-specific patterns
    - Essential features
    - Early age of onset
    - Atopy
    - Personal and/or family history
  - Important features
    - IgE reactivity
    - Xerosis
  - Associated features
    - Keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis
    - Ocular/periorbital changes
    - Periauricular lesions
    - Perifollicular accentuation

Atopic Dermatitis

- Infants
  - Facial involvement predominates early
  - Tends to spare midface
  - Oozing, crusting common
  - Exacerbated by saliva, foods
  - Extensor involvement late infancy
  - Sparing of diaper area and axilla
Atopic Dermatitis

• Childhood phase (>2 yo to puberty)
  – Distribution
    • Flexural involvement
      – Antecubital and popliteal fossae
      – Wrists
      – Ankles
    • Neck
    • Hands
    – Less crusting

Multi-Faceted Approach to Management

• Prevention
  – Restore skin barrier
  – Identifying and eliminating triggers
• Treat flare
  – Anti-inflammatory medications
  – Managing pruritus and scratching
• Super-infections
• Patient education

Prevention: Atopic Skin Care

• Daily bathing
• Synthetic detergents
• Moisturize twice daily
  – Cream or ointment preferred
  – Moisturize immediately after bathing
Managing the flare

Topical Steroids

- Used to treat inflammation during a flare
- Apply to affected areas BID
- Continue until flare is completely treated
  - Should take 7-14 days

Topical Steroid Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Steroids</th>
</tr>
</thead>
</table>
| Class I | Clobetasol propionate  
Augmented betamethasone dipropionate  
Halobetasol propionate |
| Class II | Fluocinolone  
Desoximethasone  
Betamethasone dipropionate |
| Class III | Mometasone furoate  
Triamcinolone acetonide 0.1%  
Betamethasone valerate |
| Class IV | Fluocinolone acetonide  
Fluticasone propionate |
| Class V | Hydrocortisone valerate  
Hydrocortisone butyrate  
Triamcinolone acetonide 0.025% |
| Class VI | Aclometasone  
Desonide  
Hydrocortisone 2.5% |
| Class VII | Hydrocortisone 1% |
Management of Atopic Dermatitis

Treat flare

- Factors to consider in choosing topicals
  - DURATION of lesion
    - New lesion will often respond to weaker agents
    - Chronic lesion requires stronger treatment
  - LOCATION of lesion
    - Thin skin (e.g. face, axilla, groin)
      - Higher risk for side effects, should use lower strength med
    - Thicker skin (e.g. palms, soles)
      - Lower penetration/absorption, higher strength med often required

Use of topical corticosteroids

- Class V-VI
  - Hydrocortisone 2.5%, aclometasone, desonide, triamcinolone 0.025%
- Class III-IV
  - Triamcinolone 0.1%, hydrocortisone valerate
- Class I-II
  - Betamethasone dipropionate, clobetasol, fluocinonide

Topical Steroid Vehicles

- Ointment
  - Pros: occlusive barrier, better penetration, moisturizing
  - Cons: greasy, patient non-compliance
- Cream
  - Pros: better patient compliance
  - Cons: less potent for same steroid, can sting on open skin
- Lotion and solution
  - Pros: scalp and hair-bearing areas
  - Cons: stinging
- Foam
  - Pros: scalp and hair-bearing areas
  - Cons: stinging
- Gel
  - Pros: intraoral use
  - Cons: drying, stinging
Topical Steroid Quantity

- 1 fingertip unit = 0.5 g = amount to cover palmar surface of adult hand BID
- Estimate body surface area by using your palm
  - 15 g tube to use on one palmar equivalent for 1 month

Steroid Phobia or Corticophobia

- Aubert-Wastiaux et al, 2011
  - 81% fear TCS
  - 36% are non-adherent
  - 53% warned by pharmacist of dangers of TCS
  - 55% warned by their physician of dangers of TCS

Steroid Atrophy

Epidermal atrophy
- Reversible
- Develops after months of continuous use

Striae
- Irreversible
- Develops after months to years of continuous use
- More common in adolescents

http://www.tti.library.tcu.edu.tw
Habif. Clinical Dermatology. 2010
Atrophy

- Hong et al, 2011
  - 70 children with AD, 22 matched controls
  - Compliant with TCS for at least 3 months
  - No atrophy seen

<table>
<thead>
<tr>
<th>TCS type</th>
<th>Number of patients regularly using, %</th>
<th>TCS used per month, g, mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent</td>
<td>93</td>
<td>79 (15-180)</td>
</tr>
<tr>
<td>Moderate</td>
<td>77</td>
<td>128 (59-150)</td>
</tr>
<tr>
<td>Weak</td>
<td>70</td>
<td>34 (15-30)</td>
</tr>
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</table>

Topical Calcineurin Inhibitors

- Tacrolimus ointment
  - 0.03%
    - FDA-approved ≥2 years old
    - Equivalent to class VI-VII topical steroid
  - 0.1%
    - FDA-approved ≥16 years old
    - Equivalent to class IV-V topical steroid
- Pimecrolimus 1% cream
  - FDA-approved ≥2 years
  - Equivalent to class VI-VII topical steroid

“Malignancy Risk” with TCIs

- Lymphoma and skin cancer
- FDA warning based on mice studies
  - Skin more permeable than humans
  - Lymphoma study: 26-47x the maximum recommended human dose
  - Skin cancer study: papillomas but not BCC or SCC
- Never replicated in humans
**Therapeutic Ladder**

- Narrowband UVB phototherapy
- Systemic immunosuppressants
  - Cyclosporine
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
- Avoid systemic steroids – Rapid rebound

**Omalizumab**

- Studies are conflicting
- 2 RDBPC trials showed no benefit
  - Small numbers (8 children and 20 adults)
  - Decreased IgE
  - Decreased clinical severity but no difference from placebo
- Several open label studies suggest benefit
Allergen-Specific Immunotherapy

<table>
<thead>
<tr>
<th>Baseline Relative</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Baseline</th>
<th>Placebo</th>
<th>Baseline Relative</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Baseline Relative</th>
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<tbody>
<tr>
<td>Lebron et al.</td>
<td>1.238</td>
<td>0.813</td>
<td>20</td>
<td>26</td>
<td>15.0%</td>
<td>15.0%</td>
<td>20</td>
<td>26</td>
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<tr>
<td>Park et al.</td>
<td>2.533</td>
<td>1.046</td>
<td>15</td>
<td>11</td>
<td>32.6%</td>
<td>32.6%</td>
<td>15</td>
<td>11</td>
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<tr>
<td>Lee et al.</td>
<td>1.359</td>
<td>1.586</td>
<td>10</td>
<td>13</td>
<td>24.4%</td>
<td>24.4%</td>
<td>10</td>
<td>13</td>
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<tr>
<td>Seo et al.</td>
<td>2.332</td>
<td>0.835</td>
<td>12</td>
<td>11</td>
<td>18.1%</td>
<td>18.1%</td>
<td>12</td>
<td>11</td>
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<tr>
<td>Sung et al.</td>
<td>2.299</td>
<td>0.7174</td>
<td>15</td>
<td>16</td>
<td>13.4%</td>
<td>13.4%</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>3.458</td>
<td>3.6174</td>
<td>10</td>
<td>5</td>
<td>5.3%</td>
<td>5.3%</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Park et al.</td>
<td>0.198</td>
<td>0.0302</td>
<td>107</td>
<td>55</td>
<td>57.3%</td>
<td>57.3%</td>
<td>107</td>
<td>55</td>
</tr>
</tbody>
</table>

Atopic Dermatitis

- Secondary infections common
  - *Staphylococcus aureus*
  - *Streptococcus*
  - *Herpes simplex virus*
  - *Coxsackie*

Infection Control

- Bleach baths 1-2 times weekly
  - ¼-½ cup of household bleach (6%) in tub of water
  - Soak, then rinse
- Oral antibiotics if bacterial super-infection
  - Culture for sensitivity
  - Repair of skin barrier with moisturizer and topical corticosteroid alone can reduce *S. aureus* carriage for mild cases

*concentrated bleach (8%)*
Eczema coxsackium

- 2012 CDC reported “severe and extensive” cases of hand, foot, and mouth disease attributed to coxsackievirus A6 (CVA6)
- Retrospective study of 80 patients (4 mos-16 yrs) seen 2011-2012
  - > 10% BSA in 61%
  - 4 patterns described
    - Vesiculobullous and erosive eruption 99%
    - Accentuation in eczematous dermatitis 55%
    - Gianotti-Crosti-like 37%
    - Petechial or purpuric eruption 17%
  - Delayed onychomadesis 24%

Atopic Dermatitis

- What’s new?!
Crisaborole 2% ointment

- FDA approval December 2016
- 2 years old and up
- Mechanism of action
  - Phosphodiesterase 4 (PDE4) inhibitor
    - Increased PDE4 activity in circulating inflammatory cells of AD patients
    - PDE4 inhibition in vitro reduced release of proinflammatory cytokines
- Boron-based low-molecular-weight molecule

Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults


- Efficacy and safety of crisaborole in 2 phase III AD studies
- Identically designed, vehicle-controlled, double-blind, randomized
- 2:1, crisaborole:vehicle
- BID application to all sites (except scalp)

- Baseline demographics and disease severity similar between groups
  - Age from 2-79 yo, mean 12 yo
  - 1/3 were 2-6 yo
Crisaborole

- Statistically significant decrease in pruritus at all time points compared to vehicle
- Improvement in pruritus seen quickly
Crisaborole - Adverse effects

- Application site pain 4.4% vs. 1.2%
- No serious treatment-related AEs
- Low discontinuation rate (similar to vehicle)

Crisaborole

- Low systemic absorption
- Rapid metabolism
**Dupilumab**

- Human monoclonal antibody against IL-4 and IL-13 receptors
- IL-4, IL-13 are type 2 inflammatory cytokines involved in atopic disease
- Being evaluated for asthma and chronic nasal polypsis in addition to AD
- FDA approval March 2017 for adult AD

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**Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis**

- 2 independent, randomized, double-blind, placebo-controlled, parallel-group, identical design
- 16 week treatment period

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**Dupilumab**

- Inclusion criteria
  - 18 yo
  - Moderate-to-severe AD
    - IGA 3 (moderate) or 4 (severe)
  - Not controlled adequately with topical treatment or topicals contraindicated
  - Chronic AD > 3 years
**Dupilumab**

- **Study Design**
  - 1:1:1 ratio weekly, every other week, placebo
  - Dose: 600 mg loading, 300 mg maintenance
  - Topical rescue meds permitted
- **671 patients in SOLO 1 and 708 in SOLO 2**
- **Balanced characteristics between groups**
- **Severity**: ½ moderate, ½ severe
- **Previous treatments:**
  - 33% previously treated with systemic gc’s
  - 25-31% previously treated with other systemic immunosuppressants

**Dupilumab**

**Study Endpoints**

- **Primary:**
  - Proportion of patients with:
    - IGA score 0 or 1 (clear or almost clear)
    - Decrease in IGA by at least 2 points
- **Secondary:**
  - Decrease of 75% or more on the Eczema Area and Severity Index (EASI-75)
  - Reduction in pruritus scores
  - Mean % change in EASI, SCORAD, GISS
  - Proportion reaching EASI-50, EASI-90
  - QOL
  - Anxiety/Depression scale
**Dupilumab trials**

- Rescue med use
  - SOLO 1 21%, 23% vs. 51% in placebo
  - SOLO 2 15%, 21% vs. 52% in placebo
  - Placebo group with higher rate of systemic rescue therapy and earlier
Dupilumab trials

- Adverse events
  - Most common
    - Exacerbation of atopic dermatitis
    - Injection-site reactions
    - Nasopharyngitis
  - Conjunctivitis (unspecified cause and allergic)
    - Higher in treatment group
  - No differences in laboratory values, vitals, EKGs among treatment groups

Nemolizumab

- Humanized antibody against IL-31 receptor A
- Phase II trial evaluating efficacy and safety in the treatment of moderate-severe AD
  - 4 doses evaluated
- Pruritus score was the primary endpoint
- Significant improvement in pruritus seen

https://nationaleczema.org/research/phases-drug-development/