UPDATES IN ATOPIC DERMATITIS

Amanda Hess, MMS, PA-C
President-Elect, AAPA-AAI
Arizona Asthma and Allergy Institute, Scottsdale, AZ

LEARNING OBJECTIVES

- Discuss epidemiology, risk factors, and causes of atopic dermatitis
- Discuss the pathogenesis of atopic dermatitis, including filaggrin mutations
- Discuss how atopic dermatitis influences the development of comorbid allergic conditions
- Review the clinical presentation, distribution, diagnostics, and complications of atopic dermatitis
- Review differential diagnosis and when clinicians should expect alternative diagnoses
- Review treatment of atopic dermatitis in detail, including new biologics and barriers to treatment
- Review the psychosocial aspects of the disease
- Discuss the role of both environmental and food allergies in atopic dermatitis
- Learn when to refer patients to a specialist

FINANCIAL DISCLOSURES

- Advanced Practice Advisory Board for Circassia
ATOPIC DERMATITIS

- Genetically transmitted, chronic inflammatory skin disease
- Most common chronic skin disease
- Affects up to 20% of children and 3% of adults
- Onset usually before age 5, but can develop in adulthood (20% of patients)
- Often first presenting sign of “atopic march” or “atopic triad”
- Very complex disorder caused by interaction of numerous genes with the environment

- Skin barrier defects
- Environmental and genetic factors
- Immune dysregulation
- Cutaneous microbiome
- Susceptibility of skin infections
  - 90% of patients are skin-colored with *S. aureus*, with MRSA strains becoming more common
  - “Inside-out” and “outside-in” hypotheses

PATHOGENESIS OF ATOPIC DERMATITIS

Hanifin JM et al. Dermatitis 2007

PATHOGENESIS OF ATOPIC DERMATITIS

Czarnowicki et al. JACI 2017.
Boguniewicz et al. Ann Allergy Asthma Immunol. 2018
SKIN BARRIER DYSFUNCTION

- Dysfunction in stratum corneum
  - Reduced lipid levels
  - Defects in proteases and/or antiproteases
  - Genetic defects in structural proteins
  - Physical trauma from itch-scratch cycle

Schneider et al. JACI. 2013

INSIDE-OUT OR OUTSIDE-IN?

- Does atopic dermatitis cause barrier dysfunction or does barrier dysfunction cause atopic dermatitis?
  - Inside-out: immune dysregulation and inflammation causes impaired skin barrier
  - Outside-in: impaired skin barrier causes immune dysregulation

FILAGGRIN MUTATION
CLINICAL MANIFESTATIONS

• Pruritis
  • Often worse in evening/at night
  • “The itch that rashes”

• Dry, flaky skin

• Eczematous lesions
  • Acute lesions: intensely pruritic, erythema, excoriations, exudate
  • Chronic lesions: lichenification

• History of atopy

Bieber et al. JACI. 2002.

Typical morphology and distribution

• Infants/young children: face, neck, extensor surfaces
• Older children/adults: flexural folds, chronic hand eczema

Bieber et al. JACI. 2002.
CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>CONSEQUENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective skin barrier</td>
<td>Ichthyosis, xerosis, palmar hyperlinearity</td>
</tr>
<tr>
<td>Irritants/allergens</td>
<td>Pruritis, erythema, chronic variable course</td>
</tr>
<tr>
<td>Secondary infection</td>
<td>Oozing, weeping, pain</td>
</tr>
<tr>
<td>Scratching</td>
<td>Excoriation, edema, lichenification, flaking</td>
</tr>
</tbody>
</table>

Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide deck, 2012

OTHER CLINICAL FINDINGS

- Allergic conjunctivitis
- Allergic rhinitis
  - “Boggy, pale mucosa” with turbinate hypertrophy
- Nasal polyps
- Asthma
- Food allergy
- Aspirin sensitivity

THE ATOPIC MARCH

The diagram shows the progression of atopic diseases, including eczema, food allergy, asthma, and rhinitis, over time.
TRIGGERS

- Aeroallergens
  - Animal dander, house dust mite, cockroach, pollens, molds
- Changes in temperature and humidity
- Food allergens
  - Trigger in about 30% of infants and young children with moderate to severe AD
- Irritants
  - Wool/harsh fabrics, soaps/detergents, disinfectants, cosmetics
- Microbes
  - Bacteria, viruses, fungi
- Emotional
  - Stress

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012

COMPLICATIONS

- Secondary bacterial infections
  - S. aureus with MRSA strains becoming increasingly common
- Recurrent viral skin infections
  - Herpes simplex, warts, molluscum contagiosum
- Fungal infections
  - Malassezia species
- Quality of life & emotional stress
- Behavior issues
  - Increased risk of ADHD
- Sleep disturbances

Beck et al. JACI 2009

DIAGNOSTICS

- Clinical diagnosis
- Several clinical assessment tools, but not all studied and validated
  - SCORAD Index and EASI Index have both been validated and used in several studies
- Presence of other allergic comorbidities
  - Specific IgE to relevant aeroallergens can identify potential triggers

Schneider et al. JACI. 2013
Table 2 Grading scale used for clinical scoring (EASI, SCORAD, and Severity Index).

<table>
<thead>
<tr>
<th>Grading Score</th>
<th>Score 0</th>
<th>Score 1-3</th>
<th>Score 4-6</th>
<th>Score 7-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASI</td>
<td>No scaling</td>
<td>Mild scaling</td>
<td>Moderate scaling</td>
<td>Severe scaling</td>
</tr>
<tr>
<td>SCORAD</td>
<td>No scaling</td>
<td>Mild scaling</td>
<td>Moderate scaling</td>
<td>Severe scaling</td>
</tr>
<tr>
<td>Severity Index</td>
<td>No scaling</td>
<td>Mild scaling</td>
<td>Moderate scaling</td>
<td>Severe scaling</td>
</tr>
</tbody>
</table>

Notes: The above presents the clinical evaluation criteria for EASI patients using the SCORAD and Severity Index. In this study, only mild scaling was well-assessed. Clinical assessments were performed using the EASI, SCORAD and Severity Index tools. Two dermatologists assessed the lesion parameters in the evaluations, and the final EASI, SCORAD, and Severity Index scores were obtained by averaging the scores assessed by the two dermatologists at the same time.

Abbreviations: EASI, eczema area severity index; SCORAD, SCORing AD.

The EASI scoring system is used to assess the extent of eczema. The final EASI score is the sum of the 4 region scores (0-10).

The final EASI score is determined by the extent of eczema in the following areas:
- Head/Neck
- Trunk
- Upper extremities
- Lower extremities

The final EASI score ranges from 0 to 10.
FOOD ALLERGY TESTING

- **Limited** food testing if:
  - Persistent eczema despite adequate management
  - Reliable history of immediate allergic reaction after ingestion of offending food

- Testing to foods has low specificity and needs to be interpreted carefully
  - Broad IgE food panels **NOT recommended**
  - Avoidance based on testing alone **not recommended**
  - Refer to allergist!

Schneider et al. JACI. 2013

DIFFERENTIAL DIAGNOSIS

- Allergic/Irritant Contact Dermatitis
- Seborrheic Dermatitis
- Dermatitis Herpetiformis
- Lichen Simplex Chronicus
- Tinea Infections
- Keratosis Pilaris
- Psoriasis
- Scabies
- Drug Eruptions
- Malignancy

If patient's dermatitis is not improving despite adequate treatment, must consider alternative diagnosis!

TREATMENT

- Intensity of management is dictated by severity of illness
- Goals of therapy:
  - Reduce number and severity of flares
  - Maximize disease-free periods
  - With no or minimal side effects

Schneider et al. JACI. 2013
MOISTURIZATION

- First line therapy for treatment of atopic dermatitis and seasonal xerosis
  - May be enough to control mild AD
- Impaired skin barrier function leads to enhanced water loss and dry skin
- Recommend hypo-allergenic and sensitive skin formulas:
  - Cerave, Cetaphil, Vanicream, Aveeno, Aquaphor, Eucerin, etc

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012

MOISTURIZATION: “SOAK AND SEAL”

- Recommend once to twice daily hydration with warm soaking baths for at least 10 minutes, followed by application of moisturizer
  - “Soak and Seal” or “Soak and Smear”
  - Vanicream, Cetaphil, Aveeno, Cerave, Eucerin, Aquaphor, Vaseline
  - More expensive “barrier creams” not necessarily better
- Wet wrap therapy

CERAMIDE EMOLLIENTS

- Ceramide-based emollients appear to improve barrier function and break the cycle of antigen exposure, inflammation, and water loss.
  - Often use as an adjunct to TCS therapy or “safer” alternative
  - Hylatopic, EpiCeram: Applied to skin twice daily
  - No lower age limit – safe for infants!
  - Tolerated well, safe

TOPICAL CORTICOSTEROIDS

- Mainstay of effective treatment for AD
- Applied to eczematous areas once to twice daily as needed, ideally for no more than 2 weeks
- Avoid thin-skin areas (face, skin folds)
- Use higher-potency steroid (Clobetasol, Fluocinonide) during flares
  - Apply once to twice daily for 1-2 weeks
- Once improved, switch to lower potency (Fluticasone, Triamcinolone)
  - Apply twice weekly applied to eczema-prone areas

Related to potency and duration of use

- Local:
  - Skin thinning, striae, atrophy
  - Perioral dermatitis
  - Rosacea
  - Allergic contact dermatitis
- Systemic (rare)
  - HPA suppression

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012
Lio et al. JACI: In Practice. 2014.
**TOPICAL CALCINEURIN INHIBITORS**

- Inhibit activation of key cells involved in AD
- Tacrolimus (Protopic) ointment or Pimecrolimus (Elidel) cream
- Do not cause skin atrophy and can be used in facial and eyelid eczema
- Similar effects as mid-potency topical steroid
- Side effects: Localized burning/stinging
  - No evidence that topical calcineurin inhibitors are associated with skin cancer or lymphoma

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012

**ANTIHISTAMINES**

- Often prescribed, but little evidence that antihistamines are actually helpful
  - Histamine is only one of the few mediators involved
- Because pruritus is often worse at night, sedating antihistamines may be helpful
  - Hydroxyzine, Diphenhydramine

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012

**VITAMIN D**

- Vitamin D supplementation has been associated with improvement in AD
  - Best for seasonal eczema that worsens in winter months
  - Up to 80% improvement after 1 month of Vitamin D supplementation during winter months
  - Strong correlation between vitamin D levels and severity of AD in children

Schneider et al. JACI. 2013
DILUTE BLEACH BATHS

- Intermittent soaking in dilute bleach baths have been helpful for patient with recurrent infections due to \textit{S. aureus}
  - ¼ cup bleach in tub of water
  - Recent study in November 2017 showed no benefit over plain water baths

ANTIMICROBIAL

- Topical mupirocin (Bactroban) applied as needed
- MRSA strains becoming more common

\textit{Schneider et al. JACI. 2013}
\textit{Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012}

SYSTEMIC IMMUNOSUPPRESSION

- Should only be used by providers with expertise in use of these treatment options
  - Cyclosporine most effective
  - Patients must be monitored for adverse reaction including nephrotoxicity, HTN, infection, increased risk of skin cancer and lymphoma, etc
  - Less evidence for Methotrexate, Azathioprine

- Oral corticosteroids are effective, but significant side effects
  - Should be used with caution during severe exacerbations

\textit{Schneider et al. JACI. 2013}
\textit{Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012}

PHOTOTHERAPY

- Recommended as second-line therapy by AAD
- Shown to be beneficial for disease and symptom control
  - Narrowband UV light B recommended due to low-risk profile
  - Not practical for many patients
    - Administered 2-3 times per week
    - Limited accessibility

\textit{Schneider et al. JACI. 2013}
\textit{Boguniewicz et al. JACI. 2017}
EUCRISA (CRISABOROLE)– PDE-4 INHIBITOR

- Inhibits Phosphodiesterase-4, which is overactive in AD
  - PDE4 is involved in driving cytokines and overproduction of inflammatory cells in AD
- Indicated for treatment of mild to moderate AD in patients 2 years and older
  - Clinical trials show about 50% of patients with mild to moderate AD were “clear or almost clear” at day 29 of use
- Non-steroidal
- Minimal side effects: burning/stinging at site which usually resolves


SUBCUTANEOUS IMMUNOTHERAPY

- Can be helpful in certain patients
- No strong evidence to support routine use for treatment of AD alone


DUPIXENT (DUPILUMAB)

- Anti-IL-4 and IL-13 (shared alpha subunit)
  - Indicated for moderate to severe AD in patients who have failed topical therapy (ages 18+)
  - Studies ongoing for pediatrics and adolescents
- Most studies show rapid improvement in AD

Boguniewicz et al. Ann Allergy Asthma Immunol. 2018
DUPIXENT (DUPILUMAB)

- Most studies showed rapid improvement in AD
  - 50% improvement in EASI scores after 12 weeks
  - 40% of patients were "clear or almost clear" at 12 weeks
  - 12 weeks: 50% reduction in EASI scores
  - 16 weeks: 75% reduction in EASI scores
  - When combined with TCS use, 100% of patients had at least 50% improvement in EASI scores
  - Pruritis scores improved by over 55%
  - Improvement in depression and anxiety

Boguniewicz et al. Ann Allergy Asthma Immunol. 2018

DUPIXENT (DUPILUMAB)

- Subcutaneous injection; Loading dose 600mg followed by 300mg injection every 2 weeks.
- Self-administered injection in pre-filled syringe
- No routine blood tests or monitoring
- Tolerated well: Most common side effects were allergic conjunctivitis, nasopharyngitis, headache

- Not indicated in asthma or other atopic disease... yet

Boguniewicz et al. Ann Allergy Asthma Immunol. 2018

WHEN TO CONSIDER DUPIXENT

- Patients with moderate to severe AD who have tried and failed topical corticosteroids
  - Typically most payors will want patients to try/fail topical calcineurin inhibitor, as well as Eucrisa
  - Patients who are still very symptomatic despite appropriate skin care

- Shared decision making among patient, family, and provider
**SHARED DECISION MAKING**

- Treatment goals and expectations
- Strategy in place to reach these goals
- Therapeutic options
- Risks and benefits
- Comorbidities
- Patient preference
- Socioeconomic considerations
- Education programs/material
- Written eczema action plans

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**Mild**

**BASIC MANAGEMENT**

1. Skin care
   - Moisturizer
   - Emollient
   - Ointment

2. Avoidance
   - Food
   - Environmental
   - Medications

3. Topical corticosteroids

**Moderate**

**BASIC MANAGEMENT**

1. Skin care
   - Moisturizer
   - Emollient
   - Ointment

2. Avoidance
   - Food
   - Environmental
   - Medications

3. Topical corticosteroids

**Severe**

**BASIC MANAGEMENT + TOPICAL IMMUNOMODULATOR**

1. Skin care
   - Moisturizer
   - Emollient
   - Ointment

2. Avoidance
   - Food
   - Environmental
   - Medications

3. Topical corticosteroids

**Mycology**

1. Oral antifungals

**Systemic Immunosuppressants**

1. Cyclosporine

**Corneum Occlusant**

1. Oral antifungals

**Corneum Exfoliant**

1. Topical corticosteroids

**Corneum Eliminator**

1. Topical corticosteroids

**Corneum Stabilizer**

1. Topical corticosteroids

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**PSYCHOSOCIAL ASPECTS**

- AD can have significant impact on quality of life
- Increased risk of behavioral problems and emotional distress
- Sleep disruption and increased risk of ADHD
- Fussiness, irritability, clinginess in younger children
- Higher incidence of anxiety and depression in older children and adults

Schneider et al. JACI. 2013
Arkwright et al. AAAAI Allergic Skin Diseases Committee Teaching Slide Deck. 2012

**WHEN TO REFER?**

- Any patient, especially infants and young children, with moderate to severe atopic dermatitis
  - Especially if concern for food allergy
- Any patient who is not improving with appropriate treatment
  - Moisturization, topical corticosteroids
- Patients with atypical presentations
- Adult patient with new onset dermatitis without a prior atopic history
- A patient with other comorbid allergic conditions

**Thank You!**

Any questions?

Amanda Hess, MMS, PA-C
E-mail: a.hess@azsneeze.com
Twitter: @allergyPAC