Infections and Allergies in Atopic Dermatitis: Myths versus Reality

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Clinical scenario 1:

- 11-month-old healthy girl
- Itchy, widespread eczematous plaques face, extensor extremities
- Rx: HCT 2.5%, Nutramagen
- Initially improved but now is bad again & not sleeping well
- Multiple new foods
- FH: Father had AD as a child

Mother asks you: What? Why?
- Is this an allergy to the formula or a food?
- Is there a blood test we can do?
- Should I go to an allergist for allergy testing?

According to the revised Hanifin and Rajka criteria and the American Academy of Dermatology 2014 Atopic Dermatitis guidelines, which of the following is considered an essential diagnostic feature of atopic dermatitis?

A. Family history of atopic dermatitis
B. Pruritus
C. Elevated IgE level
D. Presence since birth
E. Skin biopsy showing spongiosis
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Which of the following is the strongest risk factor for Atopic Dermatitis?

A. Family history of atopic dermatitis  
B. Living in a rural area  
C. Early introduction of solid foods  
D. Male sex  
E. A high total IgE level

Atopic dermatitis: Clinical Diagnosis

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Atopic dermatitis: Epidemiology

- Affects 20% of children & 2-3% of adults
- 60% develop AD in 1st year of life
- 90% by 5 years of age
- 10-30% of patients persists into adulthood
- Strong risk factors:
  - (1) a family history of atopy and
  - (2) the loss of function mutations in the FLG

Atopic dermatitis: Risk Factors

<table>
<thead>
<tr>
<th>Increased risk</th>
<th>No effect</th>
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<tbody>
<tr>
<td>Black race</td>
<td>Type of delivery (i.e., c/s or vaginal)</td>
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<tr>
<td>Higher level of parental education</td>
<td>Male v Female sex</td>
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<tr>
<td>Higher socioeconomic status (*some studies)</td>
<td>Timing of solid food introduction</td>
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<tr>
<td>Living in urban areas</td>
<td>Withholding of allergenic foods by infant and/or mother</td>
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Protective factors: exposure to microbial endotoxin, farm animals and dogs, unpastuerized milk consumption (*not recommended)

Unlikely: daycare, pets.

Atopic dermatitis: Biomarkers

- Most commonly associated laboratory feature = elevated total and/or allergen specific serum IgE level
  - Not present in 20% of affected individuals
  - Present in 55% of the general population
  - May be a secondary phenomenon
- Total IgE level does vary with disease severity
  - Not a reliable indicator
  - Some with severe disease have normal values
- Similar inconsistent associations:
  - Mast cell & eosinophil counts, CD30, IL-12, -16, -18, -31, thymus and activation regulated chemokine (TARC)

AD Pathogenesis: Multifactorial

- Genetic Susceptibility
- Immune Dysfunction
- Epidermal Barrier Dysfunction

Atopic dermatitis: Biomarkers

Recommendations for use of biomarkers:

- For patients with presumed atopic dermatitis, there are no specific biomarkers that can be recommended for diagnosis and/or assessment of disease severity.
- Monitoring of immunoglobulin E levels is not recommended for the routine assessment of disease severity.
  - Strength of recommendation: A
This parent is concerned that a food allergy is causing her child's atopic dermatitis. On questioning there have been no hives, no lip swelling, and no other signs of immediate hypersensitivity. What is the best next step in management?

A. Check a full food immunoglobulin E (IgE) panel
B. Check a limited food IgE panel, including peanut, soy, fish, egg, and wheat
C. Patch testing with food chemicals
D. Limited skin prick for foods
E. Treat with topical therapies and follow clinically, allergy testing is not indicated

Atopic dermatitis & Food Allergies

- 15-30% of children with moderate to severe AD also have food allergies
- “An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”
  - IgE mediated: rapid onset (1 – 6 hrs) \( \rightarrow \) Urticaria, flushing, Respiratory and/or GI symptoms, anaphylaxis
  - Non-IgE mediated: delayed onset (6 – 48hrs) \( \rightarrow \) eczematous dermatitis

- May be a trigger in a small subset of moderate-severe AD patients

Food elimination diet x 4-6 weeks

Most common: Egg, milk, peanut, soy & wheat

Older children: tree nuts, fish, shellfish

Unlikely that food is a trigger

Recommendations:
- If significant concerns for allergy are identified (ie hives, urticaria, etc) assessment can be undertaken.
- Consider limited food allergy testing (ie. cow’s milk, eggs, wheat, soy and peanut) in children < 5 yrs with moderate to severe AD if:
  - Persistent moderate–severe AD in spite of optimized topical treatment, and/or
  - History of immediate and reproducible reaction after ingestion of a specific food
Atopic dermatitis & Food Allergies

Recommendations:
• Food elimination diets based solely on the findings of food allergy test results are not recommended for the management of AD.
• If a patient has a true immunoglobulin E mediated allergy, he or she should practice avoidance to prevent potential serious health sequelae.

The mother of an infant with severe atopic dermatitis asks whether she should delay introduction of peanuts because there is a family history of eczema and food allergies. What is the most appropriate response?

A. Yes, early introduction increases the risk of developing a peanut allergy
B. Yes, given her family history she is at high risk of anaphylaxis
C. No, current evidence now supports early introduction of peanuts
D. No, current evidence shows that timing of introduction does not matter

Consensus communication on early peanut introduction in high-risk infants

• Provide interim guidance based on current evidence supporting early peanut introduction
• Learning Early About Peanut Allergy (LEAP) Trial
• 5 year RCT of 640 high risk infants ages 4 – 11 months
  – High risk – history of egg allergy, severe eczema
  – Most (542) with negative skin prick test, 98 had minimally positive responses to peanut
• Two arms – Avoidance versus peanut ingestion three times weekly

Tests: Skin Prick Test (SPT) and serum-specific IgE levels
• High negative predictive values (>95%) and low specificity and positive predictive values (40-60%)
Consensus communication on early peanut introduction in high-risk infants

• Results:
  – 17.2% (peanut avoidance grp) vs. 3.2% (peanut consumption grp) had peanut allergy at 5 years of age
  – 14% absolute risk reduction & number needed to treat of 7.1
  – 81% relative risk reduction

• Interim guidance:
  – Recommend introduction of peanut products into diets of “high-risk” infants in countries where peanut allergy is prevalent
  – Infants with egg allergy or severe eczema might benefit from evaluation by allergist or dermatologist familiar with these guidelines to assist in implementing these suggestions

Clinical scenario 1: Answers

• What? Atopic dermatitis
• Why? Father with AD, right genetics and environmental triggers
• Is this an allergy to the formula or a food? No, more likely to also have a food allergy but not the cause
• Should I go to an allergist for allergy testing? No, no reproducible reaction
• Treatment: Fluticasone cream twice daily until clear, moisturizer, once clear, reintroduce regular formula

Clinical scenario 2:

• 12-year-old boy with AD
• Thick eczematous plaques on arms and legs
• In past year, “always flaring”
• Current Rx: Cephalexin x 10 days, completed 1 month ago, hydrocortisone butyrate lotion once a day, vaseline
• Hx of furuncules but not now

Father asks you:

My wife says he needs antibiotics
His eczema is always flared up, is this an infection?

AD and Infections

• Increased susceptibility to viral, bacterial and fungal infections
  – Molluscum contagiosum
  – Herpes simplex
  – Smallpox
  – Staphylococcus aureus

Staphylococcus aureus and AD

• Highly prevalent in atopic dermatitis
  – Pooled data from 95 studies
  – Lesional skin - 70% prevalence of S. aureus colonization; odds ratio (OR) versus control: 19.74
  – Nonlesional skin - 39% prevalence of S. aureus; OR: 7.7
  – Nares - 42% prevalence of S. aureus; OR: 4.5
  – Prevalence of colonization increased with disease severity
  – Eczema clinical severity α S. aureus density
  – 100-1000-fold > density of S. aureus on lesional compared to non-lesional
  – Clinical relevance is patient dependent
  – No morbidity in most patients

Staphylococcus aureus and AD

• Barrier and innate immunity defects promote S. aureus colonization
• S. aureus derived ceramidase increases the permeability of the stratum corneum
• S. aureus produces exotoxins that act as superantigens
  – Antigen-independent activation of T-cell receptor promotes inflammation
  – S. aureus superantigens (SEB) applied to intact nonlesional skin of AD patients can induce erythema and dermatitis
• Sensitization: high levels of anti-staphylococcal IgE in AD
The father of this 12-year-old boy asks you to prescribe an antibiotic because the culture taken by his pediatrician grew *Staphylococcus aureus*. You inform the father that with the use of topical corticosteroids prescribed, the density of *Staphylococcus aureus* is expected to:

A. Increase  
B. Decrease  
C. Stay the same  
D. Increase or decrease depends on the person

**Antibiotics in Atopic Dermatitis**

- Oral antibiotics alone do not lead to satisfactory clinical improvement
- The addition of oral or topical antibiotics to topical anti-inflammatory treatments in uninfected eczema, reduces *S. aureus* density (temporarily) but does not lead to superior clinical improvement 1-4
- Both groups (TCS or TCI alone and TCS or TCI + Antibiotic) had decreased colonization rates and same clinical improvement 1-4
- Patients quickly recolonize with *S. aureus* 2
- *S. aureus* develops resistance 4

**S. aureus and Atopic dermatitis**

- Treatment of uninfected AD with topical anti-inflammatory medications improves barrier and decreases bacteria 1-3

**Antimicrobials in Atopic Dermatitis**

**Recommendation:**
- Except for bleach baths with intranasal mupirocin, no topical antistaphylococcal treatment has been shown to be clinically helpful in patients with AD, and is not routinely recommended.
  - Strength of recommendation: A/I
- In patients with moderate to severe AD and clinical signs of secondary bacterial infection, bleach baths and intranasal mupirocin may be recommended to reduce disease severity.
  - Strength of recommendation: B/II

**Wet wrap therapy in AD**

- Method to quickly reduce AD severity
- Significant flares and/or recalcitrant disease
- Technique:
  - (1) TCS or TCI
  - (2) Moist layer: Tubular bandages, gauze, cotton suit, PJs
  - (3) Dry layer
- Increased penetration, decreasing water loss, and providing a physical barrier against scratching

**S. aureus returns to baseline levels after treatment**

- Mean relative abundance of bacterial families at baseline flare and post-flare

**Topical steroids suffice to decrease bacteria**

- Both groups: TCS alone & TCS + twice weekly bleach baths led to significantly decreased bacteria and *Staphylococcus*

**Bleach baths in Atopic Dermatitis**

- RCT of children with moderate to severe *infected* AD treated with cephalaxin x 2 weeks
- Greater EASI score reduction with BB (2x/week) and intranasal mupirocin ointment (5-day/month) vs simple bathing at 3 months
- Improved clinical severity but did not eradicate *S. aureus*

**Antimicrobials in Atopic Dermatitis**

- The use of systemic antibiotics in the treatment of noninfected atopic dermatitis is not recommended.
- Systemic antibiotics are appropriate and can be recommended for use in patients with clinical evidence of bacterial infections in addition to standard and appropriate treatments for atopic dermatitis disease itself (which may include the concurrent use of topical corticosteroids).
  - Strength of recommendation: A/I and C/II

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**Graphs and tables**

- Changes in mean EASI scores over time
- Mean Proportion of Log10 Amplicon copies
- S. aureus returns to baseline levels after treatment
- Topical steroids suffice to decrease bacteria
Clinical scenario 2: Answers

• My wife says he needs antibiotics?
  — Antibiotics are not indicated because there is no clinical evidence of infection, can have side effects, and may contribute to development of resistant bacteria

• Is this an infection?
  — No, S. aureus is more prevalent on his skin because he has atopic dermatitis

• Treatment: mometasone ointment + Wet wrap therapy short term, moisturizer

Summary

• Atopic dermatitis is a chronic inflammatory skin disease with a complex pathogenesis; new insights into inflammatory pathways → new therapeutic targets

• No biomarkers yet

• Food elimination diets (including elemental formula use), and allergy testing without a history of a reproducible reaction are not recommended

• S. aureus is a known colonizer on AD skin, oral and topical antimicrobials provide no additional clinical benefit are not recommended for the treatment of routine non-infected AD flares