Food Allergy and Atopic Dermatitis (the Allergy Perspective)

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Allergy Associates of the Palm Beaches
Disclosures

- AI Immune (Sub-Investigator/Clinical Trial)
- Genentech (Speaker Bureau)
Doctor, please tell me what I can stop feeding my child?
Learning Objectives

• Apply knowledge of the basic features and patterns of atopic dermatitis in order to diagnose patients with food induced atopic dermatitis
• Identify the most common food allergens and other factors involved in atopic dermatitis
• Demonstrate understanding of how to test if food induced atopic dermatitis flares proceed and how to proceed with test results
Learning Objectives

- To be aware of new options available for treatment of atopic dermatitis
Definition

• Atopic dermatitis is a chronic inflammatory skin condition characterized by pruritus, eczematous lesions, following a relaxing and remitting course
<table>
<thead>
<tr>
<th>Essential (must be present)</th>
<th>Important (supports diagnosis)</th>
<th>Associated (nonspecific but supports diagnosis)</th>
<th>Exclusionary (excludes diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>early age of onset</td>
<td>atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)</td>
<td>scabies</td>
</tr>
<tr>
<td>Eczema (acute, subacute, chronic)</td>
<td>atopy</td>
<td>keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis ocular, periorbital changes</td>
<td>seborrheic dermatitis</td>
</tr>
<tr>
<td>Morphology—typical or atypical? Age-specific patterns:</td>
<td>personal and/or family history</td>
<td>other regional findings (eg, perioral changes, periauricular lesions)</td>
<td>contact dermatitis (irritant or allergic)</td>
</tr>
<tr>
<td>Infants and children: facial, neck, extensor involvement</td>
<td>immunoglobulin E reactivity</td>
<td>perifollicular accentuation, lichenification, prurigo lesions</td>
<td>ichthyoses</td>
</tr>
<tr>
<td>Any age group: current or previous flexural lesions; sparing of groin and axillary regions</td>
<td>xerosis</td>
<td></td>
<td>cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>History—chronic or relapsing?</td>
<td></td>
<td></td>
<td>psoriasis photosensitivity dermatoses immune deficiency diseases erythroderma of other causes</td>
</tr>
</tbody>
</table>
Lesions on Babies

Babies are commonly affected by Atopic Dermatitis. Lesions often affect the face and extensor surfaces but spare the diaper area.
Types and Locations of Lesions

Acute and Subacute

- more common in young children
- very itchy papulovesicular lesions associated with serous exudate and excoriation
- face, neck, and extensor surfaces

Source\textsuperscript{7}

Chronic

- papules, excoriation and lichenification
- flexural areas of the extremities

Source\textsuperscript{6}
Prevalence

The prevalence of AD has **tripled** over the past 30 years.

- AD affects 15-30% of children in industrialized countries
- 85% of AD presents by 5 years old
- 70% resolves by adolescence
- AD can be difficult to manage in adults
- 2-8% of cases start in adulthood
- AD affects 1-14% of adults in industrialized countries
- Prevalance- up to 25% of children and 7% of adults are affected
- Typically occurs during infancy and early childhood with onset in the 1\textsuperscript{st} year of life in 60-85% of children and 85% by 5yrs of age
- 50% of adult cases diagnosed during childhood years and 30% of childhood cases persist into adult years
Risk Factors

- Family history of atopy
- Loss of function Filaggrin gene
- Hygiene hypothesis? Inverse correlation between AD and exposure to farm animals, pets in early life, early day care, endotoxin
- Hard water association?
The Atopic March
Atopy association

- Patients with AD have higher rates of allergic diseases than the general population.
- Up to 80 percent of children with AD develop asthma and/or allergic rhinitis later in childhood.
- Ten to 20 percent of patients with AD have food-induced urticaria/anaphylaxis compared with 1 to 3% of the general population.
- In infants with eczema, the prevalence of immunoglobulin E (IgE)-mediated food allergy confirmed by double-blind, placebo-controlled food challenge (DBPCFC), except in patients with a history of anaphylaxis and positive specific IgE, ranges from 33 to 63 percent.
- AD is also associated with elevated serum IgE. A high total serum IgE level is a strong risk factor for AD in children from birth to six years of age.
Numerous studies have demonstrated an increased rate of sensitization to both food and aeroallergens in patients with AD. On average, 50 percent of children and 35 percent of adults with AD are sensitized to common allergens. However, these proportions vary widely (7 to 78 percent). Evidence of allergen sensitization is not proof of clinically relevant allergy. Confirming clinical reactivity is especially important when food allergies are suspected in young children since avoidance of food allergens can put growing children at nutritional risk.
• Infants and young children with AD are more commonly sensitized to foods (wheat and egg sensitization are most prevalent)
• Children over five years and adults are more commonly sensitized to aeroallergens (dust mite sensitization is most prevalent in both children and adults
Objective

• Who should we test for food allergy?
• How do we interpret test results in atopic dermatitis?
• How do we use elimination diets safely and effectively?
Who should we test for food allergy?
Food sensitization in AD

• Sensitization (overall)
  o Production of allergen specific IGE
  o Develops early in life
  o Does not always correlate or have clinical significance

• Sensitization in AD
  o 6x higher in patients with AD compared to healthy controls
  o Lower association with clinical reactivity in patients with AD
Food sensitization in AD

- Prevalence
  - 30-80% but around 50% in general population of patients with AD
  - Up to 66% for selected populations of patients with AD

- Regional
  - Eg. Egg sensitization 22% in Belgium and 54% in Australia
Sensitization ≠ Allergy

The diagnosis of food allergy requires demonstration of sensitization and confirmation of clinical symptoms.

- It is not uncommon to have a negative allergy evaluation in patients with moderate to severe atopic dermatitis.\textsuperscript{13d}
- SPT and IgE tests always need to be interpreted in the context of patient age and clinical context.
- Reliance on specific IgE testing alone leads to over-diagnosis of food allergy in patients with atopic dermatitis without anaphylaxis.

**Average Negative Predictive Value* = \geq 95%**\textsuperscript{20a}

**Average Positive Predictive Value* = \sim 40%**\textsuperscript{20b}

*The values are averages because the numbers can vary by allergen.
Clinical significance of sensitization

- Food sensitization ≠ clinical reactivity
- Food allergy confirmed in only 25-35% of OFC
Why should I test

• Encourage early introduction to prevent the development of IGE mediated food allergy

• Screen for IGE mediate food allergy in at risk population

• Explore possibility of food exacerbated atopic dermatitis in sever, recalcitrant AD
Prevention of IgE mediated allergy

- Early oral exposure
- Early cutaneous exposure

Tolerance
Sensitization
Prevention of IgE mediate food allergy to peanut: LEAP study

A Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Cohort Description</th>
<th>Avoidance Group</th>
<th>Consumption Group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT-Negative Cohort (N=530)</td>
<td>13.7%</td>
<td>1.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPT-Positive Cohort (N=98)</td>
<td>35.3%</td>
<td>10.6%</td>
<td>0.004</td>
</tr>
<tr>
<td>Both Cohorts (N=628)</td>
<td>17.2%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Prevention of IgE mediated food allergy to egg

• Prevention of egg allergy in patients with AD
  o Possible benefit of early egg introduction
  o High levels of egg sensitization
  o High level of IgE mediated egg allergy
Why should I test

- Encourage early introduction to prevent the development of IGE mediated food allergy

- **Screen for IGE mediated food allergy in at risk population**

- Explore possibility of food exacerbated atopic dermatitis in severe, recalcitrant AD
IgE mediated food allergy

- In general population, no screening due to poor PPV of testing

- Prevalence
  - All children with AD: 10-20%
  - Children with moderate to severe AD <5 yrs of age: 30%
  - Infants with severe eczema: 33-66% (good chance 6 months old with severe AD will have food allergy)
IgE mediated food allergy

• Implicated foods
  o Egg, milk, and peanut most common
  o Wheat soy, seafood allergy same as general population

• Risk factors for food allergy
  o Earlier onset of AD
  o Persistent AD
  o Severity of AD
• How do I know who has an IgE mediated food allergy?

• Do traditional allergy test cut off values apply to infants with AD?
Role of serum IGE testing

**Summary of 95% PPV**

<table>
<thead>
<tr>
<th></th>
<th>sIgE (kU/L)</th>
<th>SPT (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Egg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(age &gt;2)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>(age &lt;2)</td>
<td>2</td>
<td>4 (age &lt;2)</td>
</tr>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(age &gt;2)</td>
<td>15-32</td>
<td>8</td>
</tr>
<tr>
<td>(age &lt;2)</td>
<td>5</td>
<td>6 (age &lt;2)</td>
</tr>
<tr>
<td><strong>Peanut/Tree nut</strong></td>
<td>15</td>
<td>8</td>
</tr>
</tbody>
</table>
**TABLE E3.** Predictive value of IgE testing in positive or negative OFC results \(^{219-222,224-226,228}\)

<table>
<thead>
<tr>
<th>Food</th>
<th>&gt;95% Positive</th>
<th>~50% Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>slgE</td>
<td>SPT</td>
</tr>
<tr>
<td>Egg white</td>
<td>≥7</td>
<td>≥7</td>
</tr>
<tr>
<td></td>
<td>≥2 if age &lt;2 y</td>
<td></td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>≥15</td>
<td>≥8</td>
</tr>
<tr>
<td></td>
<td>≥5 if age &lt;1 y</td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>≥14</td>
<td>≥8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>≥20</td>
<td></td>
</tr>
</tbody>
</table>
Serum IgE testing

- Specificity of serum IgE testing low for infants with AD

- Role of predictive cut-off values
  - Even when 100 kU/L was used, clinical food allergy did not reach 90% for any food
  - NPV high for all decision points (NPV is very good)

- Serum specific IgE should not be used as a substitute for oral food challenge
Serum IgE testing

- 89% of food challenges in children with AD avoiding food based on sensitization were negative

- Serum IgE was not predictive of the development of peanut allergy in the LEAP study
Skin testing

- May be more accurate predictor of food allergy in infants with AD
- More data needed on predictive values
Why should I test

- Encourage early introduction to prevent the development of IGE mediate food allergy

- Screen for IGE mediate food allergy in at risk population

- Explore possibility of food exacerbated atopic dermatitis in severe, recalcitrant AD
Immediate IgE mediated non eczematous reaction

Immediate IgE mediated reaction that includes pruritus

Scratching

AD flare

Immediate IgE mediated eczematous reaction

Ingestion of antigen

0-2hrs

AD flare (IgE mediated)

Late non-IgE mediated eczematous reaction

Ingestion of antigen

6-48hrs

AD flare (non IgE mediated)

Food exacerbated AD
Frequency of Food-Induced Atopic Dermatitis

Click each circle above to see the frequency that food may be a factor in AD, characteristics of AD, and impact of AD on quality of life in children.9a

1-3% affected by food allergens
- Areas of dry skin
- Infrequent itching
- (+/- small areas of redness)
- Little impact on sleep, everyday activities, and psychological wellbeing

5-10% affected by food allergens
- Areas of dry skin,
- Frequent itching, redness
- (+/- excoriation and localized skin thickening)
- Frequently disturbed sleep
- Moderate impact on everyday activities and psychosocial wellbeing

20-33% affected by food allergens
- Widespread dry skin
- Incessant itching, redness
- (+/- excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration in skin pigmentation)
- Nightly loss of sleep
- Severe limitation of everyday activities and psychological functioning
Understand the Patient Profile

1. Food allergy symptoms like failure to thrive, vomiting, and diarrhea may be seen in infants with AD and food allergy.  

2. Food allergy is more likely to be a trigger if the skin worsening is temporally related to the introduction of a new food.

3. Food allergies are unlikely to be a trigger if the patient has periods of clear skin on a regular diet without medication.
Food exacerbated AD

• Criteria
  o Clinical history of improving of dermatitis on food removal
  o Worsening dermatitis on introduction to food
  o Proof of sensitization controversial

• Egg, milk, peanut, soy, wheat account for 90%

• 10% may be T cell mediated, not identified by testing

• Food is rarely the sole cause of AD
Atopic Dermatitis and Food Allergies

Foods Most Commonly Implicated in Children with Atopic Dermatitis

>90%: cow's milk, hen's eggs, wheat, soy, peanuts and tree nuts, fish

most commonly implicated food in atopic dermatitis in toddlers

<10%: other foods
Food exacerbated AD

- Rare isolated eczematous reactions
- 1-10% with mild/mod AD may have food exacerbation
- 5% with AD experienced late eczematous reactions during OFC

- 20-37% with severe AD
- One study showed 58% had isolated eczematous reactions
- ½ of failed challenges results in worsening eczema
Predictors of food exacerbated AD

• History and testing have poor predictive value for food exacerbated AD

• Allergy testing
  o Sensitivity and specificity of allergy testing lower for predicting eczematous reactions
  o Up to ¼ of positive challenge were associated with negative allergy testing
  o Atopy patch testing did not lead to reduction for OFC
Frequency of Food-Induced Atopic Dermatitis

Severity of eczema **increases** the likelihood of food-exacerbated AD.<sup>8</sup>
Frequency of Food-Induced Atopic Dermatitis

Treatment resistant atopic dermatitis due to food allergy is most common in young children.

About one in three young children (ages 1-3) with moderate-severe Atopic Dermatitis have IgE-mediated clinical reactivity to food proteins.\textsuperscript{10a}
History clues for food exacerbated AD

More likely:
• Correlation with food exposure
• Additional findings Suggestive of food allergy
• Earlier onset AD
• Eosinophilia

Less likely:
• Periods of clear skin on a regular diet
• Later onset AD
Challenges in Diagnoses

The diagnosis of food-induced flares is not as straightforward as IgE mediated reactions like immediate type reactions. A 4-week elimination period is necessary to show that the skin significantly improves.

If there was a history of immediate hypersensitivity with exposure, a physician observed food challenge would be appropriate.
Should we treat AD with dietary mgmt
Elimination diets

• Unselected populations
  o No benefits to elimination diets
  o Potential benefits of extensively hydrolyzed for AA formula in non breast fed infants

• Sensitized patients
  o Potential benefit of egg elimination in sensitized children (SCORAD improved in one study)
  o Can consider an elimination diet in mono-sensitized
  o May consider elemental or hypo-allergic diet in poly-sensitized
  o Must include stepwise re-introduction of foods
Complications of food exacerbated AD

- Patients with food triggered AD can develop immediate reactions after prolonged elimination.

- Main risk factor for developing an IgE mediated food allergy is avoidance of the food.

Chang et al. J ALLERGY CLIN IMMUNOL PRACT MARCH/APRIL 2016
Approach to food exacerbated AD

• Maximize treatment for AD
  o Ensure optimal skin care
  o Minimize irrigating triggers
  o Treat underlying infections

• Good skin care reduces concern for food allergy
Importance of Good Skin Care

Good skin care is required before testing for food allergy should be performed.

Parental concerns regarding food allergy decrease when the skin is better controlled.\textsuperscript{18}

However, eliminating foods is \textbf{not} a replacement for good skin care.
Before testing for food allergy, skin care **must** be optimal.

**Five Ways to Optimize Skin Care**

- **Skin hydration:** Warm and soaking 10 minute baths followed by application of a moisturizer. Moisturize at least twice daily.
- **Diluted bleach baths** – especially in patients with skin infections
- **Topical therapies** – corticosteroids or topical calcineurin inhibitors
- **Antihistamines**
- **Identify and eliminate triggers**

After implementing a good skin care regimen, re-evaluate if food allergy testing is necessary.
Elimination Testing

In infants and young children, dietary exclusion may reveal items that weren’t apparent from clinical history or rule out items that caregivers thought were a problem.

However, it may be unreliable in older patients and adults due to the placebo effect or other simultaneous changes.

Prolonged elemental and unselected elimination diets have not proven beneficial and may be harmful.
Atopic Dermatitis and Food Allergies

Testing for Cause of Dermatitis Flares in child with moderate-severe AD

Take a thorough history about diet and skin care. Proceed only when skin care is optimal.

Test the most common allergens the patient is consuming. A food and symptoms diary may be helpful to identify problematic foods.\(^{13b}\)

Positive Result: Elimination diet for 4 weeks

Improvement: Consider food allergy, perform OFC

No improvement: Food ≠ trigger, discontinue elimination diet

Positive Confirms food allergy: Begin elimination diet

Negative Reintroduce food

Source\(^{13c}\)
Approach to food exacerbated AD

- Eliminate suspicious food trigger with close follow up
  - If no improvements in AD, re-introduce food
  - If AD improved attempt oral food challenge for re-introduction to confirm diagnosis

- OFC
  - AD stable off of systemic medication and with minimal topical anti-inflammatory meds
  - Physical exam before and after OFC
  - PE 24-48hrs after OFC
  - AD should be scored with validated tool, ie SCORAD
  - Difference in SCORAD >10 significant
Retesting

Approximately how often should children with food induced atopic dermatitis flares be reassessed?

- a) 1-2 months
- b) 6-12 months
- c) 4-5 years
- d) never; the food should always be avoided

Children with food induced atopic dermatitis flares should be reassessed every 6-12 months.
• Consider emergency action plans and epi

• Complete avoidance may not be the best mgmt strategy
Summary

- Children with AD will likely benefit from early intro of allergenic foods
- More likely to have IgE mediated food allergy
- May be ingesting a food making their AD resistant to treatment
- More likely to have an IgE mediated food reaction to the allergenic foods
- More likely to have clinically irrelevant food sensitization
- Risk of developing an IgE mediated food allergy if you eliminate to food
Summary

- More studies are needed
  - Guide the intro of allergenic foods
  - Formula choice and breastfeeding advise
  - Prevalence and risk factors for food exacerbated AD
  - Role of elimination diets in AD
  - Threshold dose for maintaining tolerance and reaction
Summary

• Food challenges should be offered to determine clinical significance and guide recommendations
  o No clinical significance of sensitization
  o Importance of maintenance of food in the diet
  o Strict avoidance - risk for anaphylaxis
  o Consider strict or partial avoidance – risk for worsening eczema
Atopic Dermatitis and Food Allergies
Summary of Key Points

Atopic Dermatitis due to food allergy is most common in young children

Consider testing the most commonly implicated foods if significant atopic dermatitis remains

Make sure skin care is optimized before allergen testing

Positive testing alone does not confirm that food allergy is a significant factor in atopic dermatitis

Elimination (based on limited testing) and re-challenge is important for diagnosis

Atopic Dermatitis remains a challenging topic.
An Australian Consensus on Infant Feeding Guidelines to Prevent Food Allergy: Outcomes From the Australian Infant Feeding Summit

1. When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron-rich foods, while continuing breast-feeding.

2. All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy, and wheat products in the first year of life. This includes infants at high risk of allergy.

3. Hydrolyzed (partially or extensively) infant formula is not recommended for the prevention of allergic disease.
Clinical Commentary Review

When Should Infants with Cow’s Milk Protein Allergy Use an Amino Acid Formula? A Practical Guide

Rosan Meyer, PhD®, Marion Groetch, MSc®, and Carina Venter, PhD®

London, United Kingdom; New York, NY; and Denver, Colo
TABLE VII. Formulas suggested as first choice by guidelines

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>AAF</td>
<td>AAF</td>
<td>No specific recommendation</td>
<td>AAF</td>
</tr>
<tr>
<td>Acute urticaria or angioedema</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Atopic eczema/AD</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>BoE</td>
<td>AAF</td>
<td>AAF</td>
<td>The NIAID guidelines acknowledge that trials in BoE have shown symptom relief and endoscopic improvement in almost all children on AAF/elemental diet, though no specific recommendation on formula choice is made</td>
<td>AAF (as specified by current ESPGHAN guidelines on BoE)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Cow’s milk protein—induced enteropathy</td>
<td>EHF</td>
<td>EHF unless severe in which case AAF</td>
<td>No specific recommendation</td>
<td>EHF but AAF if complicated by faltering growth</td>
</tr>
<tr>
<td>PPES</td>
<td>EHF</td>
<td>AAF</td>
<td>Hypoallergenic formulas are recommended</td>
<td>EHF</td>
</tr>
<tr>
<td>Proctocolitis</td>
<td>EHF</td>
<td>EHF</td>
<td>No specific recommendation</td>
<td>EHF</td>
</tr>
<tr>
<td>Breast-feeding with ongoing symptoms (already on maternal elimination diet) or requiring a top-up[^*] formula</td>
<td>No specific recommendation</td>
<td>AAF</td>
<td>No specific recommendation</td>
<td>With severe symptoms that are complicated by growth faltering, a hypoallergenic formula up to 2 wk may be warranted. In many countries, AAF is used for diagnostic elimination in extremely sick exclusively breast-fed infants. Although this is not evidence based, it is aimed at stabilizing symptoms</td>
</tr>
</tbody>
</table>

DRACMA, Diagnosis and Rational for Action against Cow’s Milk Protein Allergy; NIAID, National Institute of Allergic and Infectious Diseases.

[^*]: Top-up formula is where a hypoallergenic formula is required because of insufficient breast milk or the inability to exclusively breast-feed.
Special Article

Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape

Mark Boguniewicz, MD *, Luz Fonacier, MD †; Emma Guttman-Yassky, MD, PhD ‡; Peck Y. Ong, MD §; Jonathan Silverberg, MD, PhD, MPH †; Judith Rosen Farrar, PhD ¶

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¶ Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois
* Academic Services Connection, Inc, Canandaigua, New York
<table>
<thead>
<tr>
<th>Non-lesional</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic Management</strong></td>
<td><strong>Basic Management</strong></td>
<td><strong>Basic Management + Referral to AD Specialist</strong></td>
<td></td>
</tr>
<tr>
<td>1. Skin Care</td>
<td>1. Skin Care</td>
<td>1. Skin Care + Topical Anti-Inflammatory Medication</td>
<td></td>
</tr>
<tr>
<td>- Moisturizer, liberal and frequent (choice per patient preference)</td>
<td>- Moisturizer, liberal and frequent (choice per patient preference)</td>
<td>- Apply on areas of previous or potential symptoms (aka flare)</td>
<td></td>
</tr>
<tr>
<td>- Warm baths or showers using non-soap cleansers, usually once daily and followed by moisturizer (even on clear areas)</td>
<td>- Warm baths or showers using non-soap cleansers, usually once daily and followed by moisturizer (even on clear areas)</td>
<td>- Low potency 1x-2x daily (including face)</td>
<td></td>
</tr>
<tr>
<td>2. Antiseptic Measures</td>
<td>2. Antiseptic Measures</td>
<td>- Medium potency 1x-2x weekly (except face)</td>
<td></td>
</tr>
<tr>
<td>- Dilute bleach bath (or equivalent) ≤2x/week according to severity (especially with recurrent infections)</td>
<td>- Dilute bleach bath (or equivalent) ≤2x/week according to severity (especially with recurrent infections)</td>
<td>- OR Maintenance TCI (pimecrolimus, tacrolimus)</td>
<td></td>
</tr>
<tr>
<td>- Antibiotics, if needed</td>
<td>- Antibiotics, if needed</td>
<td>- 1x-2x daily</td>
<td></td>
</tr>
<tr>
<td>3. Trigger Avoidance</td>
<td>3. Trigger Avoidance</td>
<td>- 2x-3x weekly (not an indicated dosage)</td>
<td></td>
</tr>
<tr>
<td>- Proven allergens and common irritants (eg, soaps, wool, temperature extremes)</td>
<td>- Proven allergens and common irritants (eg, soaps, wool, temperature extremes)</td>
<td>OR Crisaborole 2%¹</td>
<td></td>
</tr>
<tr>
<td>- Consider comorbidities</td>
<td>- Consider comorbidities</td>
<td>- 2x daily</td>
<td></td>
</tr>
<tr>
<td><strong>Apply TCS to Inflamed Skin</strong></td>
<td><strong>Apply TCS to Inflamed Skin</strong></td>
<td><strong>Consider acute tx for some patients to help gain control:</strong></td>
<td></td>
</tr>
<tr>
<td>Low to medium potency TCS 2x daily for 3-7 days beyond clearance [Consider TCI, crisaborole]</td>
<td>Medium to high potency TCS 2x daily for 3-7 days beyond clearance [Consider TCI, crisaborole]</td>
<td>• Wet wrap therapy</td>
<td></td>
</tr>
<tr>
<td>If not Resolved in 7 Days, Consider</td>
<td>If not Resolved in 7 Days, Consider</td>
<td>• Short-term hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

¹ Consider any patient with severe keratosis pilaris, ichthyosis, or significant dry skin as Crisaborole 2% may not be adequate and consider TCI/TCI (pimecrolimus, tacrolimus)

² Dupilumab

³ Cyclosporine A

⁴ Methotrexate

⁵ Mycophenolate mofetil

⁶ Azathioprine

⁷ Corticosteroids

Some patients treated with dupilumab may experience worsening of their AD. Consider acute tx for some patients to help gain control.
Figure 3. Some characteristics of moderate to severe atopic dermatitis. (A) Image of a 50-year-old man who has had moderate to severe atopic dermatitis for at least 10 years. In addition to the displayed lesions, he has associated atopic keratoconjunctivitis and is nearly blind in his left eye. Photo courtesy of Luz Fonacier, MD. (B) Image depicts skin atrophy on a patient with a history of severe atopic dermatitis who had used high potency topical corticosteroids to control his symptoms for years. Skin atrophy from topical corticosteroids is a rare but potential side effect of topical corticosteroids. Photo courtesy of Peck Ong, MD. (C) Image of a woman who has numerous excoriations, shown on her legs, and is heavily colonized with *Staphylococcus aureus*. Her pruritus (score 8 of 10) keeps her awake at night. Photo courtesy of Luz Fonacier, MD.
**PATIENT PROFILE: Stepping up from MILD to MODERATE AD:**
Symptomatic* despite appropriate use of low to medium potency TCS and following basic management recommendations for skin care, antiseptic treatment and avoidance of allergens and irritants.**

- Increase TCS dose or potency
- Add TCI
- Add crisaborole 2% ointment

**Options**
- 3-month therapeutic trial with reassessment at 4-8 weeks

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**PATIENT PROFILE: Stepping up from MODERATE to SEVERE AD:**
Symptomatic* despite an aggressive course of topical prescription therapy (TCS, TCI, crisaborole) for ≥ 3 wks and following basic management recommendations for skin care, antiseptic treatment and avoidance of allergens and irritants, and particularly when there is a severe and negative impact on daily activities, psychosocial health, and quality of life.**

- Phototherapy
- Dupilumab
- Systemic immunosuppressant therapy
- Cyclosporine
- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Corticosteroids

**Refer to specialist**
Consider for some patients acute Tx to help gain control:
- Wet wrap therapy
- Hospitalization

**3-month therapeutic trial with reassessment at 4-8 weeks**
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

Highlights of the Study

• This study was instrumental in the approval of crisaborole by the US Food and Drug Administration for topical treatment of mild-to-moderate atopic dermatitis in patients age ≥2 years

• At study entry
  • 86% of the patients were age 2-17 years
  • Two-thirds had moderate atopic dermatitis

• There was a high vehicle response rate, likely because of its hydrating effect

• Crisaborole is the first topical phosphodiesterase-4 inhibitor for atopic dermatitis
  • No evidence of systemic adverse events observed with oral phosphodiesterase-4 inhibitor therapy (apremilast)
Implications for Clinical Practice

• New class of topical treatment that avoids limitations with topical corticosteroids and topical calcineurin inhibitors

• Availability of this new medication should reinforce the treatment goal of minimal rash and itch, as well as minimal disease complications such as sleep disturbance
Highlights of the Study

• Crisaborole ointment is the first topical inhibitor of phosphodiesterase-4, an enzyme known to be activated in atopic dermatitis, leading to inflammation.

• In both phase 3, 28-day, double-blind, randomized, controlled studies in children as young as 2 years of age and adults with atopic dermatitis, a significantly greater number achieved clear or almost clear status with at least a 2-grade improvement using crisaborole ointment vs vehicle.

• The only treatment-related side effect that occurred in at least 1% of the more than 500 patients given crisaborole ointment in the study was application site burning or stinging, which was reported by 4.4%.
Impact on Patient Care

Many patients, families, and physicians remain concerned about using topical steroids for treating atopic dermatitis. Even for physicians who use topical steroids as the mainstay of treatment, their chronic use to maintain control and application to sensitive areas, such as the face, can be worrisome.

The only available alternatives have been the calcineurin inhibitors, which have an associated black box warning, necessitating explanation about the theoretical risk of cancer (which has not materialized) to offset the required mention by the pharmacist with dispensing. Phosphodiesterase-4 inhibitors, including crisaborole, are a welcome nonsteroidal addition, especially for use with milder disease, for sensitive skin areas, and to reduce the chronic need for steroids.
Two Phase 3 Trials of Dupilumab Versus Placebo in Atopic Dermatitis

Panel A shows the proportions of patients with the primary end point (both a score of 0 or 1 [clear or almost clear] on the Investigator’s Global Assessment (IGA; scores range from 0 to 4, with higher scores indicating more severe disease] and a reduction from baseline of 2 points or more on the IGA at week 16) among patients who received dupilumab every week, dupilumab every other week, or placebo in SOLO 1 and SOLO 2. Panel B shows the proportions of patients with the key secondary end point (which was considered to be a coprimary end point by regulators in the European Union and Japan) of an improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI-75) at week 16 in the two trials. P<0.001 for all comparisons between dupilumab and placebo. For binary end points, patients who received rescue medications or withdrew from the study were categorized as having had no response, as were those with all other missing values.
Figure 2. Secondary End Points.
Shown are the least-squares mean percent changes from baseline in the Eczema Area and Severity Index (EASI) score (Panels A and B) and in the weekly average of peak scores on the numerical rating scale (NRS) for pruritus (a key secondary end point) (Panels C and D) in SOLO 1 and SOLO 2 at 16 weeks (P<0.001 for all comparisons with placebo). The I bars represent standard errors. For the pruritus NRS, the baseline peak score was the average of the daily scores for maximum itch intensity during the 7 days immediately preceding randomization (minimum of four scores required). For continuous end points, data from patients who received rescue medications were categorized as missing at all time points after the receipt of the rescue medication; missing data were imputed with the use of a multiple-imputation method.
Highlights of the Study

- Dupilumab represents the first prospectively developed, selective immunologic agent that targets atopic dermatitis.

- The mechanism of action of dupilumab and its efficacy in atopic dermatitis as reported in this study emphasize the role of T-helper type 2 (Th2) cytokines in the pathogenesis of atopic dermatitis.

- There was remarkable improvement in objective scores of skin clearing, as well as patient-reported outcomes, such as depression and anxiety.
Implications for Clinical Practice
The availability of dupilumab should impact state-of-the-art management of adults with moderate-to-severe atopic dermatitis
  Other systemic medications are not often used because of toxicity concerns and/or because they are not approved for atopic dermatitis in the United States

Unanswered questions
  Which patients are appropriate candidates for dupilumab?
    It is not clear the requirements of insurance companies for coverage
  How long should dupilumab be continued? Will there be a relapse when stopped?
  Will some patients experience sustained remission?
  Role in children
  Significance and management of conjunctivitis
Highlights of the Study

• Dupilumab is a novel biologic that blocks both IL-4 and IL-13 whose use over 16 weeks in patients with atopic dermatitis had dramatic effects on skin inflammation, symptoms of itch, and quality of life

• Dupilumab did not function as an immunosuppressant as no increase in infectious outcomes were seen

• Symptoms of anxiety and depression were reduced as well
Impact on Patient Care

At long last, dupilumab offers the potential to treat adult patients with moderate-to-severe atopic dermatitis with a targeted therapy that yields better efficacy without the toxicities encountered with currently available systemic therapies.