Atopic Dermatitis: A Management Update

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I have nothing to disclose.

Objectives

- Discuss the immune and skin barrier dysfunction that occurs in atopic dermatitis.
- Discuss management of atopic dermatitis, including emerging treatments.
- Review the role of food allergy in AD and the limitations and pitfalls of allergy testing.
Atopic Dermatitis: Background

AD is the most common skin disorder in young children.
- Prevalence of 10-20% in the 1st decade of life.

Significant impairment in sleep and overall quality of life.


So what do I need to know about barrier dysfunction?

Skin barrier dysfunction leads to:
1. Increased trans-epidermal water loss.
2. Increased allergen penetration and allergic inflammation.

These have important implications for treatment and prevention.
Skin Barrier Dysfunction

- Skin barrier defects in skin lipids, filaggrin, and tight junctions lead to increased transepidermal water loss and increased skin inflammation.

- Leaky baby skin predicts AD:
  - Increased TEWL at Day 2 predictive of AD
    - Independent of FLGG status and parental AD
    - Lowest quartile TEWL: less risk of AD


Skin Barrier Dysfunction

1. Abnormal skin architecture
2. Reduced barrier integrity
3. Increased trans-epidermal water loss

- Tight junction defects.
- Reduced levels of stratum corneum lipids:
  - Ceramides
  - Cholesterol
  - Fatty acids

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Skin Barrier Dysfunction

- Epidermal differentiation complex on chromosome 1q21 contains genes for multiple components of the epidermal barrier:
  - Filaggrin
  - Loricrin
  - Trichohyalin
  - Involucrin

Filaggrin

- Loss of function mutations (R510X and 2282del14) associated with atopic dermatitis and asthma (in setting of atopic dermatitis).

- Eczema associated with FLG mutations presents earlier in life and is more persistent

- Initial studies examined European cohorts, but further studies with more diverse populations have identified numerous other mutations

Allergic Sensitization

- Skin barrier defects may allow for increased immunologic exposure to allergens.

Enhanced allergen penetration through an abnormal skin barrier leads to production of TSLP: thymic stromal lymphopoietin

- “master switch for allergic inflammation”
- Minimal TSLP in normal and non-lesional skin
- Increased TSLP in lesional skin

Prevention?

- Randomized controlled study of 124 infants at high risk for AD.
- Full-body emollient therapy at least once daily starting by 3 weeks of age vs no emollients.
- At 6 months of age 50% relative risk reduction in emollient group, with no adverse effects.


Hallmarks of AD

1. **Defects in the epidermal barrier function.**
   - Filaggrin defects
   - Reduced ceramide levels
   - Endogenous proteolytic enzymes
   - Enhanced trans-epidermal water loss
   - Soaps and detergents
   - Staph aureus proteases
   - HDM proteases

2. **Cutaneous inflammation**
   - Allergic
   - Mechanical
   - Infection
Treatment Goals

- Limit Itching
- Repair the skin
- Decrease inflammation

Treatment

- Eliminate exacerbating factors
- Restore skin barrier function
- Hydration
- Anti-inflammatory treatment
- Patient education
Skin Hydration: improves skin barrier function

- Guidelines recommend the consistent and liberal use of emollients and skin protectants for prevention and maintenance of the epidermal skin barrier.
- Emollients may reduce the need for topical corticosteroid use.
- Emollient and skin protectants soften the texture of skin and relieve pruritus.

Correa & Nebus, 2012

Anti-inflammatory therapy
Topical Corticosteroids

Atopic Dermatitis: Treatment

- Recalcitrant, severe AD
  - Step 4: Systemic therapy (e.g., CyA) or UV therapy

- Moderate to severe AD
  - Step 3: Mid-high potency TCS and/or TCI

- Mild to moderate AD
  - Step 2: Low-mid potency TCS and/or TCI

- Dry skin only
  - Step 1: Basic treatment: Skin hydration, emollients, avoidance of irritants, identification and addressing of specific trigger factors

TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A
* Over the age of 2 years

FIG 5. Stepwise management of patients with AD.
Practical Methods of TCS Use

- As low as you can go (or just above where they were).
- Consider thickness of stratum corneum
- “Stronger steroids” to start, with tapering to less potent CS as AD improves
- More prolonged use of less-potent preparations
- “Mix and match” of TCS and non-steroid topicals
- Wet wraps with TCS for more difficult remissions

Krakowski AC, Eichenfield LF, Dohil MA. Pediatrics 2008;122:812-824

Steroid Phobia

- 72.5% of parents worried about TCS on child's skin
- 24% admitted to not using medicines because of the worries.

Compliance/Adherence Tools

- Discussion of steroid strengths and safety
- Educational and Instructional materials
- Written action plans, Web-sites, Video training modules, Text/Email reinforcers, Apps
- Follow-up soon!
- www.eczemacenter.org

Improving Adherence

- Influence QUANTITY OF USE of TOPICALS!
  - Advise grams per week (or weeks per tube)
- Assure safety with quantity of use over certain time
Fingertip Units

One fingertip unit (FTU) is the amount of topical steroid that is squeezed out from a standard tube along an adult's fingertip.

A finger tip is from the very end of the finger to the first crease in the finger.

One FTU is enough to treat an area of skin twice the size of the flat of an adult's hand with the fingers together.

Two FTUs are about the same as 1 g of topical steroid.

Therefore, for example, say you treat an area of skin the size of eight adult hands. You will need four FTUs for each dose.

- This is 2 g per dose. If the dose is once a day, then a 30 g tube should last about 15 days of treatment.
Topical Calcineurin Inhibitors

- Anti-inflammatory medicines
  - Tacrolimus
  - Pimecrolimus

Safety update:
- Data looking very good re- no increased risks: skin cancer, lymphoma

PDE4 inhibitors

- PDE4 is a regulator of inflammatory cytokine production in AD
- Crisaborole is a non-steroidal boron based PDE4 inhibitor
  - Decreased disease severity, pruritus and other signs of AD in adults and children ages 2 and up with mild to moderate atopic dermatitis.
Dupilumab

- Anti IL-4 receptor antibody
- Inhibitor of IL-4 and IL-13 signaling.
- Approved for adult patients with uncontrolled moderate-to-severe atopic dermatitis.

Therapies in development

- **Nemolizumab**
  - Anti-IL-31, phase 2 results showed 30% itch reduction in first week
- **Tralokinumab**
  - Anti-IL-13R, phase 2: significant improvement in QOL and itch vs placebo
- **Lebrikizumab**
  - Anti-IL-13, phase 2: 50% decrease in AD area and severity when used with BID TCS for 12 weeks
- **JAK Inhibitors**
  - Phase 2 studies are ongoing, PO
- **Microbe Transplant**
  - Under study at University of CA at San Diego
Bleach Baths

TABLE 6 A Bleach Bath Primer

Explain to patients that their skin may benefit from “swimming in pool water.” Then, give them these instructions for making a pool right in their very own bathroom.

1. Add lukewarm water to fill the tub completely (aloe vera gel 40 gallons of water).
2. Depending on the size of the tub, amount of water used, add 1/4 to 1/2 cup of common bleach solution to the bath water. Any sodium hypochlorite (bleach) solution will do (for example, Clorox liquid bleach): the goal is to make a modified Dakin’s solution with a final concentration of about 0.005%.
3. Stir the mixture to ensure that the bleach is completely dissolved in the bath water.
4. Have patients soak in the chlorinated water for 5 to 10 minutes.
5. Thoroughly rinse skin clear with lukewarm, fresh water at the end of the bleach bath to prevent dryness and irritation.
6. As soon as the bath is over, pat the patient dry. Do not rub dry, as this is the same as scratching.
7. Immediately apply any prescribed medications/medicines.
8. Report bleach baths 2–3 times a week or as prescribed by the physician.

The following restrictions apply:

Do not use undiluted bleach directly on the skin. Even diluted bleach baths can potentially cause dryness and/or irritation.

Do not use bleach baths if there are any breaks or open areas in the skin (the skin of inner-erasing and burning).

Do not use bleach baths in patients with a known contact allergy to chlorine.
Bleach baths and alternatives

- ¼ to ½ cup for ½ to full tub of standard bleach (6%)
- Na Hypochlorite body wash (CLN BodyWash)
- Dilute Na hypochlorite and hypochlorous acid (Aurstat)
- Microcyn-based antipruritic hydrogel (Atrapro)

BLEACH: MAY NOT BE JUST ANTIMICROBIAL!

- Topical hypochlorite inhibits NF-κB dependent genes in keratinocytes
- HOCL: may be “anti-inflammatory”
- Topical HOCL soaks inhibited radition dermatitis, prevented ulceration (and NF-κB-driven genes)
- In aged mice: attenuated age-dependent changes, enhanced epidermal thickness and proliferation, comparable to young skin

Wet Dressings

Wet Wraps

<table>
<thead>
<tr>
<th>TABLE 7: Keeping Eczema Under Wraps: Recommendations for Applying Wet Wraps</th>
</tr>
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<tbody>
<tr>
<td>Gather your supplies.</td>
</tr>
<tr>
<td>Topically apply an ointment and/or emollient prescribed by your physician.</td>
</tr>
<tr>
<td>The wraps themselves consist of a bottom layer (and top dry layer). Gauze wrap (e.g., cheesecloth) or cotton sheets, pajamas, or long sleeves may be used. It will be necessary to have two of the material chosen. Alternatively, it is possible to use the “daddy sock” method for wrapping extremities. Simply cut a small hole in the toes of any adult-sized pair of 100% cotton socks to create a pair of tubular cotton bandages that fit easily over an extremity, can be moved up or down as needed, and can be washed and reused.</td>
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<tr>
<td>Warm water in a sink or basin.</td>
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<td>Apply the steroid ointment directly to the patient’s inflamed skin using tongue depressors or popsicle sticks (similar to how a spatula is used in cooking). Using a “spatula” helps to avoid direct contamination of the medication supply, allows large areas to be covered quickly and evenly, and prevents the caregiver from being unnecessarily exposed to topical corticosteroids.</td>
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<tr>
<td>Apply emollient to the rest of the patient’s skin.</td>
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<tr>
<td>Take a layer of the wrap (e.g., gauze or one sock) and soak it in warm water.</td>
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<tr>
<td>Wrapping any excess water until this bottom wet layer is only very slightly damp.</td>
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<tr>
<td>Wrap the affected area with the wet layer material. Make sure the wet layer is not too tight.</td>
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<tr>
<td>Immediately put the dry layer over the wet layer. Do not use plastic as the dry layer (it is too occlusive and may be a choking hazard).</td>
</tr>
<tr>
<td>Make sure the wrapped patient remains in a warm environment, which helps to promote a higher degree of humidity and ensures that the child does not get too cold as the evaporation process occurs.</td>
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<tr>
<td>Wet wraps are generally left in place overnight and may be applied for 5 to 7 days in a row. As always, follow the advice of the physician for frequency of change and duration of use.</td>
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<tr>
<td>Maintain close contact with the physician while undergoing the use of wet wraps. Report any suspected adverse effects immediately.</td>
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Wet Wrap Treatment
Wet Wrap Treatment

Wet Wraps

FIGURE 2. SCORAD on admission (blue bars) and at discharge (red bars) paired for 72 patients, sorted by SCORAD at admission (high to low). By using a paired t test, differences between SCORAD index scores at admission and discharge were significant (t, 18.93; df, 71; P < .001). Of note, the gap between the blue and red bars gets smaller from left to right, which demonstrates that the greater the severity of AD at admission, the greater the improvement.
**TABLE 1. Key points for care of AD**

<table>
<thead>
<tr>
<th>Skin care plan should include instructions for</th>
<th>Bathing daily</th>
<th>Skin cleansing</th>
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<tbody>
<tr>
<td>Skin hydration, schedule for emollient usage</td>
<td>Schedule for appropriate use of topical anti-inflammatory agents</td>
<td>Plan for control of itching and infection</td>
</tr>
<tr>
<td>Wet wrap use if prescribed</td>
<td>When to contact provider</td>
<td>Patient education tips</td>
</tr>
<tr>
<td>Simplify regimen</td>
<td>Consistent schedule for skin care and bedtime</td>
<td>Frequent moisturizing</td>
</tr>
<tr>
<td>Importance of follow-up</td>
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</tbody>
</table>
Atopic Dermatitis: Treatment

- Daily bath
- Soap free cleanser
- Pat dry
- Apply topical meds
- Cream or ointment based moisturizer
  - Cerave, new cetaphil plus ceramides
  - Vaseline occludes but does NOT add moisture
- Wet wraps, bleach baths
- Sedating antihistamines at night if necessary
  - Itch of AD is mediated by IL-31 NOT histamine

Atopic Dermatitis: Treatment

- Antihistamines
  - Little to no help
  - Sedating antihistamines may be helpful at bedtime
    - Amitriptyline, periactin
- Phototherapy
  - Second-line treatment
  - For patients over 12 yrs with greater than 30% BSA involvement
Adjuvant Therapy

Pruritus is one of the defining features of AD, with associated scratching that leads to excoriated, often superinfected lesions, bleeding, lichenification, and/or nodular changes. In addition, pruritus can cause significant sleep disturbance and affect the patient’s and caregiver’s quality of life.78 Identifying and removing trig-

Atopic Dermatitis: Treatment

- Mild cleansers with pH 5.5 to 6.0 to protect acid mantle of the skin—

  - Protective acid mantle of skin decreases skin colonization by bacteria and plays a role in permeability barrier homeostasis/stratum corneum integrity.
    - SCCE exhibits a neutral pH optimum.
    - Normal skin pH 5-5.9
  - Stratum corneum pH is also important for generation and degradation of the lipid lamellae.
    - B-glucocerebrosidase and sphingomyelinase exhibit low acid pH optimum
      - Washing skin with soap causes an increase of the pH by 3 units for more than 90 minutes and has been shown to thin the SC in healthy and nonlesional AD skin. (Cork, J All Clin Immunol, 2006)
  - Avoid emollients—skin surface lipids-damage lipid lamellae
  - Use emollient soap substitutes
    - Generic aqueous cream, Aveeno cream and wash, Balneum Plus cream and wash, Lipobase cream, Oilatum cream and bath.
Atopic Dermatitis: Treatment

Systemic antibiotic therapy
- For wide-spread secondary infection only
  - First or 2nd generation cephalosporins or semisynthetic penicillins for 7-10 days
    - Clindamycin for allergic patients
    - Macrolide resistance
  - Maintenance therapy should be AVOIDED

Other topical treatments
- Epiceram
  - Rx ceramide cream
- Hylira
  - Hyaluronic acid replacement
- Atopiclair
  - Rx device
- Atrapro Hydrogel
  - Bacteriostatic and moisturizing
Sleep Disruption

- Cover skin to reduce skin damage from night time scratching.
- Optimize Sleep Hygiene
- Wet wraps as necessary
- Consider a sedating antihistamine or 2 mg of melatonin.
  - 2mg melatonin in kids 2 and over has been shown to improve SCORAD score & decrease sleep latency by 30 minutes in AD.

Role of food allergy?

“I know that something in Jamie’s diet is causing his eczema!”

“I want my child skin tested to all foods so that we can find out the root cause of her eczema!”

“What foods should I eliminate to help clear Rachel’s skin?”
Food Allergy and Atopic Dermatitis

New data shows that concern about food allergy is magnified compared to actual risk.

- Allergy skin prick tests and specific IgE testing have a very high false positive rate
  - Amplified in kids with atopic dermatitis

When to test??

“Testing for food allergy is recommended only for children younger than 5 years old who have had persistent AD despite optimized therapy or a reliable history of an immediate reaction to a food.”

- From update of 2012 AD practice parameters AND NIAID Food allergy guidelines

Lio et al. J Allergy Clin Immunol Pract Volume 2, Number 4
In the absence of anaphylaxis, serum food-specific IgE testing cannot be used to determine the need for a food elimination diet, especially in children with atopic dermatitis.
Sensitization ≠ Allergy

• Don’t contribute to the crisis of LOSS OF ORAL TOLERANCE!

  ▪ First do no harm.

  ▪ Do not embark on food allergy work-up unless able to perform oral food challenges.

  ▪ If recommending an elimination diet in AD, must have capability to perform challenge.

Algorithm for FA evaluation in AD

For children who meet above criteria that have a positive diagnostic test:

- Diagnostic food elimination diet for 4 weeks
  - No improvement: stop elimination

  - Improvement: Consider food allergy, perform a an oral food challenge
  - Negative OFC: reintroduce food
  - Positive OFC: continue elimination diet

Bergmann et al. J Allergy Clin Immunol: In Practice, Volume 1, Number 1
Environmental factors
Atopic Dermatitis: Pathogenesis

Environmental Factors

- **Aeroallergens**
  - Exposure is an AD risk factor and increases severity.
  - Intranasal exposure to aeroallergens has been shown to cause itching and skin lesions in adults with AD. (Cezmi, J All Clin Immunol 2006)
  - APT with aeroallergens on uninvolved skin causes eczematoid skin lesions in a subset of adults with AD. (Darsow, Allergy 2004)
  - House dust mite reduction measures have been shown to improve AD.
    - Produce cysteine proteases which breakdown corneodesmosomes and enhance TH2 cytokine production.
    - T cells specific for Der p 1 have been isolated from AD skin lesions. (Cezmi, J All Clin Immunol 2006)

- **Microorganisms**
  - AD patients are prone to recurrent bacterial, fungal and viral skin infections
  - Susceptibility to local infection in AD is far greater than in other diseases, like psoriasis, with defective skin barrier function
    - 30 vs 7% (Christophers, Arch Dermatol Res 1987)
  - AD skin has been shown to be deficient in antimicrobial peptides (Ong, N Engl J Med 2002)
    - Upregulation of TH2 cytokines
Atopic Dermatitis: Pathogenesis

- Environmental Factors: Microbes
  - *S. aureus*: 90% of AD patients are colonized (vs 5-30%)
    - Most patients experience a worsening of skin disease after infection
    - Superantigen: Non-specifically stimulates T cells and IgE specific responses
      - Many AD patients make specific IgE against staphylococcal superantigens; levels correlate with disease severity. (Leung, J Clin Invest 1993)
      - Superantigen induces a competitive glucocorticoid receptor (GRβ) that interferes with the normal binding of corticosteroids to GRα and their therapeutic effect. (Hauk, J All Clin Immunol 2001)
  - Staphlococcal exfoliative toxin (protease) cleaves Desmoglein 1 and disrupts desmosomal structure.
  - Binding of *S. aureus* is enhanced by skin inflammation
    - Treatment with topical corticosteroids or TCIs reduces cutaneous *S. aureus* burden in AD

Thank you!