Severe Atopic Dermatitis: An Algorithm
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Atopic Dermatitis: Stepwise approach to Severe Atopic Dermatitis:

1. Fix the barrier
2. Evaluate and treat any root cause
3. If still recalcitrant consider systemic therapy
Atopic Dermatitis

Genetics: Defective Skin Barrier

Food/Nutrition

Contact Allergy

Environment

Infection Immunodeficiency
Step 1: Fix The Barrier

Prevention of the Atopic Dermatitis Inflammatory Cascade

1. Disrupted barrier (FLG mutation or dryness from cleansing/environment)
2. Allergen and irritant influx
3. Inflammatory T cell responses initiated by keratinocytes (e.g. TSLP) and dendritic cells

Emollient therapy improves skin barrier and blocks inflammatory cascade
Step 1: Fix The Barrier

Atopic dermatitis and skin disease

Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

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Study Design: RCT of 124 infants at high risk for Atopic Dermatitis (AD)

Intervention: Emollient moisturizing within the first 3 weeks and continuing for 6 months vs NO Emollient.

- USA: sunflower seed oil, Mineral Oil/Lanolin/Petrolatum or emollient cream
- UK: sunflower seed oil or paraffin

- BOTH groups advised to avoid fragranced soap, use gentle cleansers, no bubble baths or baby wipes on the skin.

Outcome (by age 6 months):
  22% of those actively moisturized developed AD
  43% of Control group developed AD
Application of moisturizer to neonates prevents development of atopic dermatitis

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Tokyo, Tokushima, Hiroshima, and Osaka, Japan

Study Design: RCT

Intervention: Emollient started at 1 week

- 59 moisturized with thick Moisturizer:
  Ingredients: Glycerin, xylitol, Behenyl alcohol, Dimethicone, squalane, jojoba oil, isostearic acid peg-60 K and metaphosphoric acid sodium hydroxide, phenoxyethanol, tocopheryl, water, glyceryl stearate acid PEG-5 glyceryl carberomer.
- 59 received petrolatum but unclear if they used it.
- Children followed out for 32 weeks.
Outcome

**Intervention Group:**

- 19/59 in treatment arm developed AD
- 28/59 Controls
- Higher stratum corneum hydration in treatment arm
- No difference in rate of allergic sensitization to Egg
- No difference in *Staph Aureus* colonization
Therapeutic Algorythym
- the bottom line -

Step 1: Fix The Barrier
Emollients and washing

- Limit bathing time to 5 minutes or less (2-7 times weekly)
  - If there is a strong environmental component, then bathe daily
  - NO WASHCLOTHS
  - Moisturize within 4 minutes of bathing to retain benefit

- Use Gentle Cleansers: Dove® fragrance free Soap/Cetaphil® gentle skin cleanser/ Cerave® Wash are examples

- Lubricate with thick emollients: Tell them which EXACT ONE
  - Examples include Cerave® moisturizing Cream, Aveeno® Healing ointment, Cetaphil Restoraderm®, Aveeno® eczema therapy, Vaseline ointment, Exederm® cream

The skin is immunosuppressed in active atopic dermatitis

- Antimicrobial peptides (Cathelicidin LL37) is down regulated in atopic dermatitis
- Up to 80% of children with atopic dermatitis are colonized with *Staphylococcus Aureus*
- When the atopic dermatitis is treated, the antimicrobial peptides come back!
- When the atopic dermatitis is scratched, it often becomes infected!

*British Journal of Dermatology* 2006 155, pp1275–1278
Hand Foot and Mouth (and Butt)

• DDX:
  – Eczema herpeticum: BUT this should be more clustered and only in places of past atopic dermatitis
  – Varicella: BUT the lack of truncal involvement would be unusual.

Enteroviral Infection
• Classically Coxackie A16
• Coxackie A6 is becoming more common and can be more exuberant and widespread
• CDC alert from 2012
• The acral predominance of true vesicles is the key

**Pediatric Bottom Line:** Atopic skin is immunosuppressed so it can be superinfected with many different pathogens

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6112a5.htm
What if they are still flaring despite your plan?

Further Testing is reasonable

**Food Testing:**

- **Positive IgE food tests**
  - Indicates presence of IgE antibody NOT necessarily clinical reactivity
  - Great sensitivity (approximately 90%)
  - Poor Specificity (many false positives)

- **Negative prick test or specific IgE to food**
  - Essentially excludes IgE antibody (very good negative predictive value)
Labs to Consider in Severe or Unusual Atopic Dermatitis

- CBC with Differential
- Zinc, Vitamin D
- Albumin, Pre-albumin
- Immunoglobulin Levels (IgG, IgM, IgA, IgE)
- B and T Cell markers and function to evaluate for congenital immunodeficiency
- Diptheria, pneumococcal and tetanus antibodies
Find the Root Cause: Major Causes of Eczema Flares

- Humidity/season changes: Affect the Barrier
- Infection: Remember the skin is immunosuppressed
- Contact Allergies: We put a lot of allergenic chemicals on the defective barrier
- Environmental Allergies: The defective barrier allows the body to become sensitized too easily
- Foods: these children are atopic so they are more likely to be allergic
- Nutrition and Immunodeficiency
- Non compliance or running out of med
When Good Skin Care is Not Enough
Use the Asthma Model

Flare Plan:
• Topical steroids Daily to BID for 1-3 weeks
• **Bottom Line:** Once the spots are flat and just discolored, stop the medication

Maintenance Plan:
• MILDE: Just Good Skin Care
• MODERATE: Topical steroid ointment or compounded medication 3-5 times per week OR Topical calcineurin inhibitor on areas that commonly flare
• SEVERE: Use a mid Potency topical steroid either undiluted or mixed with moisturizer 3-5 times per week on areas that flare OR Topical calcineurin inhibitor on areas that commonly flare
• **Bottom Line:** Find the least amount needed to **prevent a flare**
What should I do for major flares?

- Treat signs of infection
- Wet wrap with low-mid-potency topical steroid
- Make sure no obvious topical or environmental contactants
- Treat locally flared areas with higher potency medication
- Systemic anti-inflammatory agents or immune modulators
- NOT Oral steroids
Wet Wrap Therapy in Children with Moderate to Severe Atopic Dermatitis in a Multidisciplinary Treatment Program

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Aurora and Denver, Colo

- Wet Wrapped with triamcinolone (most commonly)
  - 10-15 minute bath
  - Apply steroid
  - Wet gauze with dry elastic over top
  - Applied for 2-4 hours
- Mean SCORAD decrease from 50 to 15
Atopic Dermatitis has a dramatic negative effect of Quality of Life

• 60% of patients have difficulty Sleeping and with daily social activities
• 23% of children with behavioral issues (5% controls)
• Atopic care of patients with severe AD takes 2-3 hours per day for the family
• Children with AD have lower school performance and difficulties socially.

Therefore: We must balance the risks of the Medications and the Risk of not treating
Systemic Alternatives for Atopic Dermatitis in Children

- **Light Therapy:** Narrow Band UVB: darker skin patients
- **Dupilumab?** IL4/13 blockade
- **Methotrexate**
  - **Pros:** Longterm safety data in children, can maintain therapy for years, Pulmonary/Liver toxicity rare
  - **Cons:** Nausea (alleviated by Subcutaneous), potential risk of lymphoma
- **Azathioprine**
  - **Pros:** High efficacy, perhaps disease modifying
  - **Cons:** Data for Squamous Cell carcinoma, potential long term toxicity

hwww.nejm.org
Drugs. 2009;69(3):297-306
Systemic Alternatives for Atopic Dermatitis in Children

- **Cyclosporine**
  - **Pros:** High efficacy, fast acting
  - **Cons:** A lot of blood draws, longterm toxicity, can only use for a limited time
- **Mycophenolate Mofetil**
  - **Pros:** Easy to use, little lab work
  - **Cons:** Potential for longterm toxicity (lymphoma)

**FDA Alert:**
- **Lymphoma and Malignancy**
  - Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients.
  - In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed
**Table III.** Strength of recommendations for the management and treatment of atopic dermatitis with phototherapy and systemic agents

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Phototherapy (all forms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Home phototherapy</td>
<td>C</td>
<td>III</td>
<td>27</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>B</td>
<td>I-II</td>
<td>34-43</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>B</td>
<td>II</td>
<td>33,44-51</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>B</td>
<td>II</td>
<td>33,42,52-56</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>C</td>
<td>III</td>
<td>34,57,58</td>
</tr>
<tr>
<td>Interferon gamma</td>
<td>B</td>
<td>II</td>
<td>59,60</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>B</td>
<td>II</td>
<td>4,35</td>
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<tr>
<td>Systemic antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• None, if noninfected AD</td>
<td>B</td>
<td>II</td>
<td>64-67</td>
</tr>
<tr>
<td>• For infected AD</td>
<td>A</td>
<td>II</td>
<td>64-67</td>
</tr>
<tr>
<td>• Concurrent topical steroid treatment during oral antibiotic course</td>
<td>C</td>
<td>III</td>
<td>No clinical trials</td>
</tr>
</tbody>
</table>


Methotrexate Studies in Children

- 40 Children randomized to MTX or Cyclosporine (El-Khalawany et al.)
  - Showed equal decrease in SCORAD at 12 weeks
  - Equal mild side effects

- 31 children treated (Deo et al.)
  - 75% with significant benefit (more than 50% improvement)
  - Only used low dose
Periorificial Dermatitis

• Small red papules around the mouth>nose>eyes
• The distribution is characteristic and there is not much else which does this!
• Risk factors include: inhaled and topical steroids
• They get worse with steroids!!
• Treatment: topical metronidazole +/- oral erythromycin or if age appropriate doxycycline
• Treatment takes 3-6 weeks to work
Goals and Objectives

Diagnostic Consideration in Severe Atopic Dermatitis?

- Humidity changes, infections, environment, nutritional deficiency, immunodeficiency, noncompliance, foods

When should I start systemic therapy?

- Remember to balance the effects of the atopic dermatitis with the side effects of the meds