Hot Topics in Pediatric A/I:
Atopic Dermatitis

Lynda Schneider, MD
Associate Professor of Pediatrics
Harvard Medical School
Children’s Hospital Boston

Disclosures:
Lynda Schneider, MD
Astellas – Investigator
NIH/NIAID/DAIT (Atopic Dermatitis Vaccinia Network and Atopic Dermatitis Research Network)

This presentation will include discussion of OFF LABEL uses tacrolimus ointment, fluticasone cream/ointment.

Learning Objectives:
- Describe the most recent clinical research findings in pediatric eczema
- Apply recent advances in pediatric allergy/immunology

Outline
- Atopic Dermatitis
  - Pathology/Genetics
  - Vitamin D
  - Treatment
  - Mental health
  - Predictors of Success
  - Practice Parameters

What goes wrong in AD?
Normal epidermis: a protective barrier
- The stratum corneum: a protein-lipid matrix with filaggrin, ceramide, and sphingosine
  - Barrier against water loss and allergen/microbe entry

Defect in Epidermal Barrier Function in AD
- Filaggrin loss-of-function mutations (RS01X and 2282del4): associated with ↑ risk of AD, asthma associated with AD
- US PEER study
  - 27.5% Caucasians
  - 5.8% AA

Palmer CN et al. Nature Genetics, 2006; Weidinger S et al. JACI, 2008
Margolis DJ, Andrea J Apter, JACI 2012;131; 912-917
The persistence of AD and filaggrin (FLG) mutations in a US longitudinal cohort

Claudin-1 expression is reduced in AD

Stratum Corneum + Tight Junctions
2 barrier structures

Correlation between serum 25-hydroxyvitamin D levels and severity of AD in children

Clinical Implications

Atopic Dermatitis: A Practice Parameter Update 2012

• Summary statement 4. The clinician should know that atopic dermatitis has become widely accepted as a disorder that is at least in part initiated by skin barrier defects. These barrier defects can be acquired or genetic.

• Summary statement 12. The clinician should be aware that atopic dermatitis is characterized by reduced skin barrier function, which leads to enhanced water loss and dry skin; therefore the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. (D)

Change in IG A score

<table>
<thead>
<tr>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 1 (worse)</td>
<td>1 (17%)</td>
<td>1</td>
</tr>
<tr>
<td>0 (same)</td>
<td>4 (67%)</td>
<td>5</td>
</tr>
<tr>
<td>- 1 (better)</td>
<td>4 (80%)*</td>
<td>5</td>
</tr>
</tbody>
</table>

Total 5 6 11

*p<0.05


Pilot study of 1000 IU Vitamin D for AD in eleven Boston children in winter

Association of vitamin D receptor gene polymorphisms with severe atopic dermatitis in adults

<table>
<thead>
<tr>
<th>Gene</th>
<th>Control (%) n=204</th>
<th>AD (%) n=265</th>
<th>P-value</th>
<th>Permutated P corr</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>26.6</td>
<td>21.2</td>
<td>0.040</td>
<td>0.11</td>
</tr>
<tr>
<td>T</td>
<td>19.0</td>
<td>21.9</td>
<td>0.24</td>
<td>0.64</td>
</tr>
<tr>
<td>G</td>
<td>44.6</td>
<td>49.8</td>
<td>0.09</td>
<td>0.42</td>
</tr>
<tr>
<td>A</td>
<td>41.0</td>
<td>34.5</td>
<td>0.030</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Heine G et al British J Dermatol; 2013/in press

Clinical Implications
Atopic Dermatitis: A Practice Parameter Update 2012

Vitamin D

- Summary statement 29. Patients with atopic dermatitis may benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.


Anti-inflammatory Treatment

AD Flare

Topical Steroid Application

Days 7-14: Low potency – face
Mid-high potency

Aim for RARE FLARES

For patients with frequent flares

AD Flare

Treat

Taper

Recurrence of flare

Proactive (OFF LABEL) usage 2 to 3 times weekly to areas typically affected by AD

- Fluticasone propionate cream or ointment
- Topical tacrolimus


Local conversion of Vitamin D in skin drives AMP expression

INFγ, TGFβ1, 1-αOHase, 25D3, 1,25D3, PTH, PTHrP, PTH1R, Cathelicidin

Schaefer et al. JCI 2006

Liu et al. Science 2006

Muehleisen et al. Science Transl Med 2012

Clinical Implications

Atopic Dermatitis: A Practice Parameter Update 2012

Vitamin D

- Summary statement 29. Patients with atopic dermatitis may benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.


Heine G et al British J Dermatol; 2013/in press
**Proactive treatment of eczema (OFF LABEL)**

- Cost-effectiveness of tacrolimus ointment: twice-weekly maintenance treatment vs. standard twice-daily reactive treatment of exacerbations from a third party payer (U.K. National Health Service) perspective.
    - Twice weekly maintenance more cost effective than standard twice daily reactive treatment

**Proactive treatment of eczema (OFF LABEL)**

- Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials.
    - Fluticasone propionate and tacrolimus are more efficacious to prevent AD flares than vehicle
    - Fluticasone may be more efficacious than tacrolimus although study designs differ
    - 4.5% of children in one fluticasone study showed biochemical evidence of adrenal suppression
  - Clinical Implications: Consider proactive therapy

**Mental Health Comorbidity in AD**

- Cross sectional study comparing No eczema to children with eczema
  - 2007 National Survey of Children's Health
  - Questionnaire to parents:
    - Parental description of severity of eczema

**Mental Health Comorbidity in AD**

- Mental health care usage:
  - No eczema 7.89%
  - Eczema 12.12%
  - P < .0001
- Mean number of days of adequate sleep decreases as eczema severity increases:
  - No eczema 6.09
  - Eczema 5.22
  - P<.0001

**Mental Health Comorbidity in AD**

<table>
<thead>
<tr>
<th>Mental health condition</th>
<th>No Ecz</th>
<th>Mild</th>
<th>P value</th>
<th>Mod</th>
<th>P value</th>
<th>Sev</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>1.66</td>
<td>.001</td>
<td></td>
<td>1.76</td>
<td>.0004</td>
<td>4.35</td>
<td>.0001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.47</td>
<td>.003</td>
<td></td>
<td>1.97</td>
<td>.0006</td>
<td>2.81</td>
<td>.003</td>
</tr>
<tr>
<td>Depression</td>
<td>1.14</td>
<td>.003</td>
<td></td>
<td>1.18</td>
<td>.0007</td>
<td>2.12</td>
<td>.003</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>1.08</td>
<td>.005</td>
<td></td>
<td>1.82</td>
<td>.0159</td>
<td>3.90</td>
<td>.0016</td>
</tr>
<tr>
<td>Autism</td>
<td>1.15</td>
<td>.016</td>
<td></td>
<td>3.25</td>
<td>.0003</td>
<td>7.41</td>
<td>.0001</td>
</tr>
</tbody>
</table>

aOR, Adjusted odds ratio.

**Infant eczema, sleeping problems and mental health at 10 years of age**

- Prospective population based cohort study in Germany (LISA-plus)
- Relationship between eczema within the first 2 years, infant sleeping problems and mental health at 10 years
- Logistic regression modeling

**Mental Health Comorbidity in AD**


Infant Eczema, Sleeping Problems and Mental Health at 10 yrs. of age

- 1578 children with complete info
- 266 (24%) had physician diagnosed eczema within the first 2 years
- 92 (6%) had sleep problems due to pruritus
- 1162 never had eczema nor sleep problems


Infant Eczema, Sleeping Problems and Mental Health at 10 years of age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional problems</td>
<td></td>
</tr>
<tr>
<td>- Infant sleep problems</td>
<td>2.40 (1.32 – 4.39)</td>
</tr>
<tr>
<td>- Infant eczema with sleep problems</td>
<td>2.63 (1.20 - 5.78)</td>
</tr>
<tr>
<td>Conduct problems</td>
<td></td>
</tr>
<tr>
<td>- Infant eczema with sleep problems</td>
<td>3.03 (1.01 - 9.2)</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td></td>
</tr>
<tr>
<td>- Infant Eczema</td>
<td>1.78 (1.02 – 3.09)</td>
</tr>
<tr>
<td>- Ever Eczema</td>
<td>2.23 (1.34 – 3.37)</td>
</tr>
</tbody>
</table>


Infant eczema, sleeping problems and mental health at 10 yrs of age

- Sleep disturbance in infant eczema due to itching may be one factor in the development of future mental health problems
- Clinical Implications
  - Treat AD aggressively to improve sleep
  - Monitor for sleep disturbance
  - Refer to psychologist or sleep specialist if needed


Atopic Dermatitis: A Practice Parameter Update 2012

Quality of Life and Emotional Stress

- Summary statement 42. The clinician should recognize that atopic dermatitis has a significant impact on patient and family quality of life and patients have an increased risk for psychological distress. The clinician should ask about stress and emotional factors, which may cause exacerbations and have been found to induce immune activation as well as trigger pruritus and scratching. (C)
- Summary statement 43. The clinician should assess for sleep disturbances. Sleep may improve with treatment of inflammation, but the clinician may also consider therapeutic agents or referral to a sleep specialist or psychologist in severe cases, or when sleep does not improve in remission. (C)


Sleep Interventions

- Relaxing, consistent bedtime routine
- Cool temperature
- Wraps or wet underlayer of pajamas
- Sleep-suits/modified pajamas so hands/feet covered
- Treat the inflammation and infection


Topical Steroid Phobia

- Questionnaire given to AD patients at out-pt dermatology practices (5 university; 53 private practice in France
- 208 questionnaires (144 parents)
- Results
  - 80.7% fears about topical steroids
  - 36 % admitted non-adherence

Topical Steroid Phobia

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Variable</th>
<th>β-Coefficient (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>Need reassurance</td>
<td>0.67 (0.36–0.99)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Belief / representation</td>
<td>TCS pass into the bloodstream</td>
<td>0.63 (0.28–0.98)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Origin / communication</td>
<td>Prior adverse event</td>
<td>0.67 (0.03–1.31)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Belief / representation</td>
<td>Discrepancies about quantity</td>
<td>0.34 (0.01–0.66)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Strategy of action</td>
<td>Treat oneself the shortest time possible</td>
<td>0.61 (0.30–0.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Poor adherence</td>
<td>0.53 (0.12–0.94)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>


Review of BCH AD Center

- Overall 71% of patients had improvement in EASI score
- EASI score improvement correlated with:
  - Decreased parental concern with treatment side effects
  - Decreased itching
  - Better patient sleep


Summary

- Skin barrier defects play a role in AD
- Vitamin D induces antimicrobial peptides and may be helpful in AD although more studies are needed
- In patients with frequent flares consider proactive therapy (OFF LABEL)
- Patients with AD (especially severe AD) have an increase in mental health and sleeping disorders

Boston Children’s Hospital Atopic Dermatitis Center

- Multidisciplinary outpatient program for children with refractory AD
- Half day session per week
- Treatment team:
  - Nurse Practitioner
  - Psychologist
  - Nutritionist

www.childrenshospital.org/atopic

AD Center – Predictors of clinical success

- Improved parental ability to follow treatment regimen
  - If the family follows the plan and puts on the meds without worry of side effects the patient will get better
- Severe AD and younger age of treatment initiation
  - Patient with severe AD have a greater capacity for improvement
  - AD patients tend to improve with time
  - Older children have scratching and non-adherence behaviors which are more difficult to change than younger children