Severe Atopic Dermatitis in Children

Elaine C. Siegfried MD
Professor of Pediatrics and Dermatology
Director, Division of Pediatric Dermatology
Saint Louis University
Overview

• Indications for systemic therapy
• Pretreatment evaluation
• Current choices (especially methotrexate)
• The pipeline
Early therapeutic intervention and disease control may impact progression and comorbidities.
Successful Topical Treatment

Most Important Factors

- Apply bland emollient BID-QID.
- Avoid complex topicals.
- Use adequate quantities of medication.
Ubiquitous, Non-Essential, Avoidable Topical Allergens

- Fragrances
- Kathon
- Cocamidopropyl betaine
- Propylene glycol
- Disperse blue
- Class A and B corticosteroids
- Adhesives
# Safe and Effective Use of Topical Medications in Children

*How Much, How Often, How to Monitor?*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Quantity</th>
<th>Frequency</th>
<th>Safety Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>corticosteroids</td>
<td>15-60 gm/mo (based on age/weight/potency)</td>
<td>15 d/mo</td>
<td>AM cortisol</td>
</tr>
<tr>
<td>vitamin D analogs</td>
<td>100-200 gm/mo</td>
<td>BID</td>
<td>spot urine Ca:Cr screen</td>
</tr>
<tr>
<td>calcineurin inhibitors</td>
<td>100-200 gm/mo</td>
<td>BID</td>
<td>tacrolimus peak</td>
</tr>
</tbody>
</table>
Monitoring Topical Medication Use

- Do not give automatic refills.
- Check pharmacy dispensing records.
- Examine tubes at every visit.
Monitoring Topical Medication Use

Avoid pound jars.

1 tablespoon = 15 gm
Food Allergy

- Greatly overdiagnosed in children with AD
- Allergen-specific skin testing and serum IgE are highly sensitive, but have low positive predictive value.
- Elimination diets should be approached cautiously to avoid unnecessary restrictions.
- Blind panel food allergy testing and avoidance of foods in the absence of a suggestive history is not recommended.

Vitamin D and Atopic Dermatitis

182 Peer Reviewed Publications Since 2000

• Epidemiological, immunological clinical data
• Congenital deficiency carries increased risk
• Low levels inversely associated with severity
• Randomized trials support supplementation

Microbiome
Metagenomic Systems Biology

• Characterize the normal microbiome
• Define disease-associated dysbiosis
• Identify microbe-host interactions (’omics):
  transcriptomics, proteomics, lipidomics, immunomics, metabol-omics (e.g. clostridial short chain fatty acid butyrate modulates Treg production)

Cutaneous Microbiogeography

• Distinguishable from other epithelia
• Site-specific topography
  – bacterial: sebaceous, folds, broad/flat
  – fungal: *Malassezia* predominates, except feet
• Microbial-associated molecular patterns (MAMPS)
  – *S. epi* enhances innate barrier immunity and limits pathogen invasion.
  – *S. aureus* triggers T-cell mediated inflammation.

Dysbiosis in Atopic Dermatitis

Pathogenesis & New Therapeutic Strategies

• Bacterial diversity is associated with disease control.
• Increases in *S. aureus* and *S. epi* are associated with disease severity.
• Some strains of *S. epi* produce mediators toxic to *S. aureus* growth and biofilm formation

Organic Oils and the Microbiome

- Organic oils contain saturated and unsaturated lipids.
- Some saturated fatty acids encourage Malassezia overgrowth.
- Excess unsaturated fatty acids may induce inflammation.
- Olive oil has been used as a standard in vitro culture media for Malassezia.
- Nondigestible mineral oil is a triglyceride-free alternative.
- No data on the impact of other organic oils on cutaneous microflora.

Atopic Dermatitis
Beyond Topical Therapy
Topical Treatment Failure

- Excessive use of topicals
- Inability to use topicals
  - Acceptance
  - Comprehension
  - Time requirement
Look for evidence of primary immune deficiency. ("Immune Dysregulation Dermatitis")
Immune Dysregulation Dermatitis

**Differential Diagnosis**

- STAT3 Hyper IgE
- Netherton syndrome
- Wiskott Aldrich
- Leiner phenotype – Omenn, SCID
- IgA deficiency
- IgM deficiency
- NEMO ectodermal dysplasia
- DOCK 8 deficiency
- Familial hypertryptasemia

- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)
- WHIM Syndrome
- GATA2 deficiency
- PLAID

"Not Hyper-IgE"
but immunocompromised; consider immunomodulating > myelotoxic treatment
grouped vesicles/crusts, “buckshot” erosions, often periorbital and perioral
Eczema Herpeticum Incognito

Similar predilection for face (especially periorbital & perioral) but without obvious vesicles.
Eczema Herpeticum Incognito
A Diagnostic and Therapeutic Challenge

- Severe extrinsic AD
- Face, periorbital involvement
- Strong family history of recurrent HSV
- Vitamin D deficiency
- Antiviral-controlled eczema flares
- *Risk of thymidine-kinase resistance*

Eczema Herpeticum Incognito
Confirming the Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV 1 Serology</td>
<td>91.67%</td>
<td>60.00%</td>
</tr>
<tr>
<td>PCR</td>
<td>37.50%</td>
<td>95.00%</td>
</tr>
<tr>
<td>Viral Culture</td>
<td>33.33%</td>
<td>95.00%</td>
</tr>
</tbody>
</table>

Treating Eczema Herpeticum

- Nucleoside analogs acyclovir, valacyclovir, famciclovir: Short-course/high dose vs. daily prophylaxis
- Failure-to-respond, culture +: special request MICs
- Thymidine-kinase resistant HSV*
  - “Difficult, albeit not uncommon.”
  - Increasing reports following prolonged therapy
  - Sensitive strains have a biologic advantage over resistant strains; use short-course/high-dose
  - Valacyclovir & famciclovir: better bioavailability

*Rich Whitley, personal communication
Treating Eczema Herpeticum

- Vitamin D
- Oral zinc sulfate
- Topicals- calcitriol, cidofovir, green tea extract (Veregen), tetracaine (Viractin)
- IV Cidofovir (nephrotoxic)
- Off-label raltegravir
- Pipeline
  - novel nucleoside analogues: valomaciclovir, FV-100
  - DNA polymerase inhibitors: oral liposomal cidofovir, tenofovir, brincidofovir
  - helicase-primase inhibitors: amenamevir and pritelivir


De SK, Hart JC, Breuer J. Herpes simplex virus and varicella zoster virus: recent advances in therapy. Curr Opin Infect Dis. 2015 Dec;28(6):589-95
Baseline Evaluation

• Personal of family history of frequent infections (OM, sinusitis, pneumonia, frequent Strep, recurrent HSV)
• Surveillance throat/skin swabs for occult Strep colonization
• Surveillance skin scrapings for HSV PCR, culture; consider HSV serology
• If suggestive, begin immune assessment.
Immune Assessment

- Quantitative immunoglobulins (M, G, G subclasses, A, E)
- ImmunoCAPS
- Serologic response to immunizations
  - Diphtheria
  - Tetanus
  - 23 serotype Pneumococcal titers < 1.3
    - ≤6 yr: >50%
    - >6 yr: >70%
  - Haemophilus Influenza b
- Toll-like receptor function
- Mannose-binding lectin level
- Complements
- Lymphocyte Immunophenotyping
- Lymphocyte Proliferation
  (cytokine panel, IL-17)
Systemic Treatment Options

- None FDA-approved
- No established guidelines for dosing/monitoring
- Level 3 evidence-based Rx:
  - **myelosuppressive**: cyclosporine, azathioprine, mycophenolate mofetil
  - **cytostatic**: methotrexate
  - **immunomodulating**: IVIG, IFN-γ, emerging targeted therapy
- Abundant expert opinion
- No long-term safety/efficacy data

Risks and benefits must be carefully weighed on a case-by-case basis, especially for biologics.
Rapid Response

- Hospitalization
- Cyclosporine
Hospitalization

- Requires trained staff
- IV medication not a prerequisite
- Intensive skin care: whirlpool, wet wraps
- Observation, behavioral intervention
- Daily skin care education
  - Process
  - Quantity
  - Frequency
- Problematic labs (e.g. AM cortisol)
- Coordinated multispecialty care:
  Allergy, ENT, GI, Child Life, Social Services
It's a Team Effort
There it is

The 'I' in team.

Hidden in the 'A' hole.
Safe, Efficient Wet Wraps

Sewing for Kids

Unique, tailor-made wraps ease skin treatments

The treatment of severe skin disease may involve “wet wraps,” which are applied immediately after a bath and application of petroleum jelly. A layer of damp fabric holds moisture on the skin and a waterproof outer garment retains the moisture for a longer time than would petroleum jelly alone.

But there was a small problem in administering wet wraps to children. “Wet wrap garments are commercially-available for adults but aren’t made for kids,” Siegfried said.

So she recruited Jo Ridenhour, a volunteer in Glennon’s Dana Brown Neonatal Intensive Care Unit who also does fine and practical sewing as a hobby. Ridenhour was intrigued by a bulletin-board notice seeking volunteers to make the special garments.

After discussing patients’ needs with Siegfried, Ridenhour revised existing garment patterns to make tops and bottoms in a range of sizes for infants and children.

The inner layer of the tops and bottoms look like long underwear and are made of pre-washed cotton with no bleaching, dyes, buttons, snaps or elastic. The outer layer is white nylon and styled after an athletic warm-up suit. The garments are held up with drawstrings.

Glennon provided fabric which Ridenhour cut according to her patterns. She requested assistance from members of St. Louis-area sewing associations and set up shop for a day in a bank’s community room.

“About 25 women brought their sewing machines and came and went during the day,” Ridenhour said. “Some women took pieces with them to finish at home. Dr. Siegfried seemed pleased with what we came up with.”

The hospital also stocks silver-impregnated silk pajamas, which do not have irritating seams, buttons or elastic, for patients to wear after wet wraps are removed.

“It was wonderful!” Siegfried said. “The volunteer-made garments are a unique and valuable benefit that our kids take home and use to help them control flares after they leave the hospital.”
Maintenance Treatment Options

• **Immunosuppressive**
  – other considerations: cost, formulation, dosing frequency, provider experience

• **Immunomodulating**
  – possibly safer alternative for children with evidence of immune deficiency.
Methotrexate

The Most Time-Honored Systemic Agent

- USFDA approved in 1959
- 12 labelled indications (incl. psoriasis)
- 23 off-label indications (incl. asthma, not AD)
- Short and long-term pediatric data
  - JIA registry
  - scleroderma
  - ALL
- Convenient, inexpensive

Methotrexate

Possibly More Well Tolerated in Children

• Adverse effects
  – Nausea, anorexia (12%)
  – Liver function test elevation (9%)
  – Rare stomatitis
  – Rare hypersensitivity (?preservative)
  – No hepatic fibrosis or pneumonitis in JIA

• Liver biopsy for high risk patients
  (obese, diabetic, alcohol-using adults)
Maximizing Methotrexate Efficacy

- Starting dose: 0.5 mg/kg/wk
- Check MTX PG in non-responders at wk 12 (Avise PG; Exagen Diagnostics)
- <30 nmol/L: ↑ PO dose or change to SQ
- Repeat 8 wk after every dose increase

MTX Response Rates: Overall – 83%

- Atopic Dermatitis N=30 (65%): 77% Responders, 23% Non-Responders
- Psoriasis & Overlap N=16 (35%): 94% Responders, 6% Non-Responders
Off-Label, Commercially Available Options

- Anti-CD20 (rituxumab)
- Anti-IgE (omalizumab)
- Anti-IL1 (anakinra, canakinumab, rilonacept)
- Anti-p40, IL12/23 (ustekinumab)
- Anti-IL17 (secukinumab)
The Dawn of the Decade of Eczema

AD Pipeline (US)

Height of bars indicates number of therapies in development

Pipeline Immune Pathway Targets

- PDE-4
- chymase
- eosinophils
- SHIP1 activator
- di-homo-\(\gamma\)-linolenic acid
- JAK
- TSLPR

- IL-4
- IL 12/23
- IL-13
- IL-17
- IL-31

Pipeline Immune Pathway Targets
Phase 3 data

- **PDE-4**
  - apremilast* (Otezla®; Celegene)
  - 2% crisaborole oint** (Eucrisa ®; Pfizer)

- **IL-4**
  - dupilumab* (Regeneron/Sanofi)

*adults
**adults and children down to age 2
2% Crisaborole Cream

- **Eucrisa® (Pfizer)**
- Boron-based PDE4 inhibitor
- USFDA approved 12/14/16
- Indication: mild-moderate AD, age ≥2 years
Development of Draft Guidance for Industry on New Therapeutic Agents for Atopic Dermatitis in Children and Adolescents