Childhood Rashes: What’s New and What’s True

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Urticaria ‘multiforme’
- Favors ages 2 months – 3 years
- Annular/polycyclic wheals
- Often angioedema of hands/feet & face
- Individual lesions last <24 hours, but often have a transient dusky purplish hue upon resolution


Urticaria ‘multiforme’
- Pruritus and dermatographism common
- Fever in ~half
- URI/other viral illness > vaccine, drug, mycoplasma, strep
  - Often a “double hit”, e.g. URI + amoxicillin
- Responds to antihistamines, but often requires higher doses and combination therapy


Causes of acute urticaria in children presenting to the ER
- Unknown (64%)
- URI/other infection (23%)
- Drug (8%)
- Food (3%)
- Bee sting (2%)

Konstandinou et al Ped All Immunol 2011; Rees et al JAMA Pediatr 2013

Why the new name – isn’t this just URTICARIA?
YES!
but
- Acute urticaria in infants/young children is often strikingly annular & looks “scary”
- Misdiagnosis as erythema multiforme and serum sickness-like reactions run rampant
- Useful in interactions with colleagues convinced it is erythema multiforme

When in doubt…

- Outline the lesions in pen and see how they evolve
  - Can give an antihistamine to speed up the process

Differential diagnosis of urticaria ‘multiforme’

- Erythema multiforme
  - Smaller, fixed lesions – last several days or longer
  - Central dusky areas that may lead to blistering/erosion, NOT clearing
  - Oral erosions common
  - Usually no facial/acral edema

Mycoplasma pneumoniae-induced (rash and) mucositis [MI(R)M]

- Mean age 12 y (most often 5-18 y)
  - Male/female ~2:1
  - <10% recur
- Prodrome of cough, malaise, and fever x ~1 week
- Prominent mucosal erosions/ulcers, vesiculobullae
  - Oral (~95%), ocular (~85%), urogenital (~65%)
- Cutaneous involvement sparse or absent in ~80%
  - Acral/extremity predominant > scattered widespread
  - Targets (often atypical & papular), vesiculobullous, macules/papules

Don’t forget coxsackie A6!

Lesions around > inside mouth

Mycoplasma pneumoniae-induced (rash and) mucositis [MI(R)M]

- Clues to etiology
  - Preceding respiratory symptoms
  - Radiographic pneumonia
  - ESR ≥35 mg/dL
- Diagnosis of M. pneumoniae
  - Mp PCR + from oropharynx (or bullae)
  - Anti-Mp IgM antibodies elevated/increasing
  - Cold agglutinins (in 50-70% after 7-10 d)
- Treatment
  - Antibiotics for lung infection (eg azithromycin)
  - ?Systemic corticosteroids, IVig

Sandhu et al Lancet Infect Dis 2017
Canavan et al JAAD 2015
Olson et al Pediatrics 2015
Prindaville et al Ped Derm 2014
Rock et al J Ped 2014
CVA6 in 2 brothers: what a difference some eczema makes

\[\text{Eczema coxsackium}\]

**Rat bite fever**

- Fevers, polyarthritis, and an acral eruption
  - Macules/papules, petechiae, vesiculopustules
- *Streptobacillus moniliformis* or (in Asia) *Spirillum minus*
  - Culture difficult; PCR possible
- Begins 3-10 days after rat bite or scratch

\[\text{Tx: penicillin, ceftriaxone, doxycycline}\]

**Differential diagnosis of urticaria ‘multiforme’**

- Acute hemorrhagic edema of infancy
  - Facial/acral edema + fever + annular, but lesions are fixed and purpuric

**Differential diagnosis of urticaria ‘multiforme’**

- Kawasaki disease
  - Facial/acral edema, polymorphic eruption can be urticarial
  - Higher, more persistent fever & sicker child
  - Conjunctival injection, oropharyngeal changes, lymphadenopathy

**A new Kawasaki rash: psoriasiform eruptions**

- Well-demarcated, pink, scaly plaques
  - Subset had crusting or fine scale
  - Less diaper are involvement
  - Median onset day 8 (range, 4-54 days)
  - Duration 2-18 months

**New AHA Guidelines: evaluation of incomplete Kawasaki disease**

\[\text{Evaluation of Kawasaki or incomplete Kawasaki disease}\]

1. Unilater al heart involvement
2. Cardiac lesions
3. Age < 5 years
4. Prolonged fever
5. Conjunctivitis
6. Oral stomatitis
7. Cutaneous lesions
8. Palmar/Plantar changes
9. Lymphadenopathy
10. Nodular scle roangitis
Differential diagnosis of urticaria ‘multiforme’

- ‘Serum sickness-like reaction’
  - Individual lesions may last several days or longer
  - Higher fever, prominent acral edema, arthralgia/arthralgias
  - Histologically similar to urticaria, no vasculitis
  - Usually triggered by an antibiotic, classically cefaclor, now more often amoxicillin
  - Functional definition: requires prednisone therapy (~2 weeks to avoid rebound)

Childhood urticaria

- **Acute urticaria/urticaria ‘multiforme’**
  - 1-year period prevalence of 1-3%
  - >15% by age 10 y
  - Usually lasts 1-2 weeks with viral trigger, but may linger as long as 6-12 weeks
- **Physical urticaria**
  - Check for DERMATOGRAPIHSM!
  - Consider cold urticaria
- **Chronic ‘spontaneous’ urticaria**
  - Classic definition: regularly x ≥6 weeks
  - Prevalence of 0.2-0.7%

Chronic ‘spontaneous’ urticaria in children

- Median age ~8 years
- Median duration 3-5 years
- Etiologies similar to those in adults
  - Autoimmune in ~30-50%
    - Anti-FcεR/IgE antibodies, detectable via basophil histamine release test (or basophil activation test)
    - Parasites, esp. if residence in travel to endemic locations
    - Food allergies are rarely the cause (but often suspected by parents)

Chronic urticaria in children: don’t overinvestigate!

- Let history and physical exam direct the evaluation
- Check for dermatographism, other physical urticarias
- First-tier labs: CBC with differential, ESR/CRP ± UA
- Consider basophil histamine release/activation assay
- Consider thyroid studies/autoAb, tissue transglutaminase Ab
- Skin biopsy if individual lesions last >24 hours, tenderness, or purpura
- Consider periodic fever syndromes if fever, eye/joint symptoms

Avoid undertreatment and oversedation!
Urticaria in children: treatment

- First-line: scheduled low-sedating, long-acting H1 antihistamine(s)
  - Often need more than standard dose or >1 agent
  - Cetirizine/levocetirizine especially effective
- Approved ages for long-acting antihistamines
  - Levocetirizine, desloratadine, fexofenadine: ≥6 months
  - Cetirizine, loratadine: marketed OTC for ≥2 years
- Add sedating H1 antihistamine at bedtime as needed
- Possible benefit of added H2 or leukotriene receptor antagonist (if aspirin/NSAID-sensitive)

Chronic urticaria in children: treatment

- Considerations for refractory disease
  - Dapsone
    - Especially if neutrophil-dominant infiltrate
  - Omalizumab (anti-IgE monoclonal antibody)
    - FDA approved for chronic urticaria in ages ≥12 y
  - Low risk of anaphylaxis
  - Mycophenolate mofetil, [cyclosporine]
  - IVlg
  - AVOID prednisone

Common rashes: myths and reality

Molluscum: ‘the bump that rashes’

- Retrospective study of 696 patients with molluscum
  - Mean age 6.5 y (range, 7 mos-17 y)
  - Atopic dermatitis (37%) assoc with higher # of MC lesions
- Molluscum dermatitis in 39%
  - 51% FAO vs 32% FAO
  - # of MC lesions T over next 3 months in 32% not treated vs 23% treated with topical steroidal, vs 16% if no derm

Gianotti-Crosti syndrome-like/”id” reaction to molluscum

- 34 patients (5%) in our series
- Pruritic eruption of monomorphic, erythematous papules/papulovesicles separate from MC lesions
  - Extensor arms & legs (94%) > face, trunk
  - Occasionally initially unilateral on trunk, like unilateral latemorthermic exanthem
  - Responded to mid potency topical CS
- Associated with inflamed MC in 65%
- Usually heralded resolution of MC
  - Median duration ≤5 weeks after onset

Update on molluscum epidemiology & treatment

- Epidemiology
  - Affects 15-20% of children by 10-15 years of age
- Natural history
  - Duration range 12 months (range, several months to 4 years)
  - 30% last >18 months, ~15% last >2 years
- Imiquimod for molluscum?
  - 2 large, industry-sponsored, unpublished ‘failed’ randomized controlled trials in 2006 showed lack of efficacy

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Comorbidities in pediatric psoriasis: psoriatic march?

- Increased prevalence of obesity
  - 30-50% in children/teens with mod-sev psoriasis, compared to ~15% in general population
  - Often central adiposity, precipitating diagnosis of psx in >90% of patients
- Metabolic and functional lipid abnormalities
- Annual screening guidelines for pediatric psx patients
  - Blood pressure
  - BMI (body mass index)
  - Additional testing for DM, dyslipidemia, and fatty liver based on weight and other risk factors
  - Arthritis screen (joint pain/stiffness/swelling, limp)
  - Screen for anxiety, depression, substance abuse

AAD guidelines on topical therapies for AD: summary of A/I recommendations

- Use of moisturizers
- Use of topical corticosteroids
  - Including proactively for maintenance
- Use of topical calcineurin inhibitors
  - Including as steroid-sparing agents, proactively for maintenance, and off-label in children <2 years of age

X Do not routinely use topical antistaphylococcal antibiotics
  - Don’t help
  - Can lead to allergic contact dermatitis, bacterial resistance

AAD guidelines for AD

- Use of moisturizers
- Use of topical corticosteroids
  - Including proactively for maintenance
- Use of topical calcineurin inhibitors
  - Including as steroid-sparing agents, proactively for maintenance, and off-label in children <2 years of age
X Do not routinely use oral nonsedating antihistamines in the absence of other conditions such as urticaria or allergic rhinoconjunctivitis

AAD guidelines for AD

- Use of moisturizers should be an integral part of treatment
  - Strength A, level of evidence I
  - Increase skin hydration, barrier function, and time to relapse
  - Decrease excoriation, pruritus, signs of AD, and frequency/amount of medications required
- Apply moisturizer soon after bathing to improve skin hydration
  - Strength B, level of evidence II
  -Immediate or with 30-min delay increases hydration, but bath alone decreases hydration

Moisturizers:
  “a cornerstone of AD therapy”
Are “fancy” moisturizers better?

- Few head-to-head trials between specific products
- Studies have not shown superiority of:
  - Rx glycyrrhetinic acid-containing hydrolipid cream* vs Rx 3:1:1 ceramide:cholesterol:free fatty acid cream* vs OTC petrolatum-based ointment
  - Rx palmitoylethanolamide-containing cream* vs OTC oil-based cream

Ideal agent: safe, effective, inexpensive, free of fragrances/irritants/potential sensitizers

Eichenfield et al JAAD 2014
Draelos Cosmet Derm 2009
Miller et al J Drugs Derm 2011
Evagelista et al Int J Derm 2014

Individualized approach to moisturizer/vehicle selection

- Ointments
  - Less stinging!
- Creams
  - Less greasy!

Moisturizer tips

- Lotions have a high water content and are less ideal for patients with xerosis
- Go for the big jar, but use a clean ‘scoop’ to prevent bacterial contamination

What about oils? – “I only use natural products”

- RCT: virgin coconut oil (VCO) vs mineral oil in children with mild-moderate atopic dermatitis (n=117) x 8 weeks
  - SCORAD ↓: 68% for VCO vs 38% for mineral (p<0.001)
  - Transepidermal water loss (TEWL) ↓: 70% for VCO vs 35% for mineral
- RCT: VCO vs virgin olive oil (VOO) in adults with atopic dermatitis (n=52)
  - SCORAD ↓: 47% for VCO vs 30% for VOO (p=0.004)
  - Staph aureus colonization ↓: 95% for VCO vs 50% for VOO (p=0.003)

Coconut oil: ~90% saturated FAs, 60% medium-chain FAs \( \Rightarrow \) decreased TEWL, antimicrobial

Olive oil: ~20% saturated FAs, high oleic acid \( \Rightarrow \) increased stratum corneum integrity, may induce inflammation, ‘feeds’ Malassezia

Sunflower seed oil: high linoleic acid \( \Rightarrow \) increased stratum corneum integrity and hydration

Mineral oil: (cyclo)alkanes \( \Rightarrow \) decreased TEWL, no “food” for Malassezia (and actually “natural” – from fossils of algae/plankton)

Can moisturizers prevent AD?

- Randomized controlled trials in neonates with a parent/sib with AD/atopy
  - Oil, cream/gel or ointment moisturizer applied daily to entire body (total n=124) \( \Rightarrow \) 50% relative risk reduction vs moisturizer-free controls at 6 months (p=.017)
  - Emulsion-type moisturizer applied daily (total n=118) \( \Rightarrow \) 32% risk reduction vs controls at 32 weeks (p=.012)
What do you advise the parents of this 6-month-old girl with widespread eczema about bathing frequency?

A. Twice a day  
B. Daily  
C. Every other day  
D. Twice a week  
E. Weekly  
F. Limited sponge bath 1-3x/week

**Bathing practices in AD: frequency and duration**

- There is no standard for the frequency, type, or duration of bathing in patients with AD
  - Very few objective data – strength C, level of evidence III
  - 3 prospective studies comparing daily to < daily bathing; 2 found significantly > mean % in SCORAD in daily group; other smaller study showed similar % in SCORAD
  - Up to once daily, warm water, 5-10 min (up to 20 if acutely inflamed)
  - In a recent survey, daily bathing in AD patients was recommended by:
    - 71% of dermatologists (SPD, Maine Derm)
    - 51% of allergists (AAAAI)
    - 21% of pediatricians/family practitioners (in Maine)

**Bathing practices in AD: cleansers & additives**

- Limited use of nonsoap cleansers
  - Neutral/low pH, hypoallergenic, fragrance free
- Against use of bath oils/additives*, acidic spring water, or water softening

*Exception of bleach baths

**Benefits of bathing**

- Removes ‘gunk’; crust, scale, irritants, potential allergens, excess bacteria
- Provides hydration when followed by medication/moisturizer
- May improve penetration of topical medications

**Staphylococcus aureus in atopic dermatitis**

- Present on dermatitic lesions in ~90% and normal-appearing skin in ~75% of patients
  - More Staphylococcus, less diversity during flares
  - Increased staphylococcal adherence to keratinocytes
  - Failure to produce antimicrobial peptides (e.g. defensins, canthelicidins)
- Exacerbates AD via heightened immune responses to bacterial antigens/superantigens
- Topical corticosteroid, TCI, or NBUVB treatment reduces S. aureus colonization better than antimicrobial agents

**‘Bleach baths’ in AD**

- Initial placebo-controlled RTC (n=31)
  - Moderate to severe atopic dermatitis, ages 6 months to 17 years, with clinical signs of superinfection
  - Bleach baths* twice weekly + intranasal mupirocin 5 days/month x 3 months
  - Mean EASI reduction 57%, vs 18% with placebo (p=.004)
  - No change in proportion of patients with bacterial colonization

*¼ cup household bleach per ½ full standard bathtub
~1 teaspoon per gallon water

Kong et al. Genome Res 2012  
Travers et al. J All Clin Immunol 2010  
Eichenfield et al. JAMA 2014  
Cardona et al Ped Derm 2015; Sarre et al JEADV 2015  
Cao et al. Ped Derm 2015  
Hang et al. Pediatrics 2009  
Cardona et al Ann Allergy Asthma Immunol 2016  
Kim et al Asia Pac Allergy 2012  
Kameyoshi et al Allergy 2008
More on “bleach baths” in AD

• No disruption of skin barrier function/TEWL/pH
• Variable results in small RTCs x 4-8 wks; no significant reduction in S. aureus colonization
• Microbiome analysis in RTC of fluticasone alone vs fluticasone + bleach baths 2x/week x 4 weeks in children <5 y old with AD
  – At baseline: ↑ all bacteria/S. aureus but ↓ diversity in AD lesions vs nonlesional skin and control patients
  – After either treatment, AD lesional skin had ↓ bacterial density and ↑ diversity, becoming similar to nonlesional skin

Hon et al. J Derm Treat 2016
Gonzalez et al. JAAD 2016

Don’t forget about Group A Strep

• Accounts for ≥20% of bacterial skin infections in patients with AD
  – Can mimic eczema herpeticum
• Patients more likely than those with S. aureus infections to:
  – Be febrile
  – Have facial/periorbital involvement
  – Be hospitalized

Sugerman et al. Pediatr Derm 2011

Pediatric periorificial dermatitis

• Mean age ~6 y
• ~60% with topical or inhaled steroid use as trigger

Goel et al. Pediatr Derm 2015

Treatment of periorificial dermatitis: a delicate balance

Rosacea Periorificial dermatitis Irritant dermatitis

• Topical metronidazole
• Oral azithromycin, erythromycin, doxy
• Topical sodium sulfacetamide, azelaic acid
• Topical (or oral) ivermectin

• Topical pimecrolimus, tacrolimus

Noguera-Morel et al. JAAD 2017

“Pustules on noses, think demodicosis” Andrea Zaenglein, MD

• For active AD, daily use of an agent with appropriate potency and duration to CLEAR the skin
  – Higher for thicker/exuberant & acral AD
  – Lower for thinner, intertriginous, & periorificial AD

Friedman et al. Dermatol Pract Comp 2017
Topical corticosteroid therapy for AD
### Treatment of active eczema

- **Daily use of topical corticosteroid**
  - High-level maintenance to "hot spots"
  - Proactive intermittent use of topical corticosteroid and/or TCI when clear

### Low-level maintenance
- Daily emollient use to all skin

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### New evidence supporting proactive maintenance in AD

- Residual subclincal inflammation is present at previous sites
- Proactive maintenance upon ‘induction of remission’ reduces rates of flares and increases number of flare-free days
  - Strength A, level of evidence I
  - Pooled relative risks of flares in metaanalysis
    - With fluticasone 2 days/week: 0.46 [95% CI, .38-.55]
    - With tacrolimus 2-3 days/week: 0.78 [95% CI, .60-1.00]
- Twice weekly fluticasone for up to 40 weeks had no skin side effects, no adrenal suppression in two 16-week trials

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### Topical crisaborole (Eucrisa™) ointment for AD

- Inhibitor of phosphodiesterase 4 (PDE4)
  - PDE4 degrades cAMP and leads to cytokine release
- RCT in 1522 patients (age ≥2 y) with mild-moderate AD, applied BID x 4 weeks
  - Clear/almost clear with ≥2-grade improvement:
    - Crisaborole 31-33%
    - Vehicle control 18-25% (p <0.04-0.001)
    - Stinging/burning at application site in ~5%

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### Topical tofacitinib for AD

- Janus kinase (JAK) inhibitor
  - Blocks JAK-STAT pathway of cytokine signaling, including IL-4
- RCT in 69 adults with mild-moderate AD, applied BID x 4 weeks
  - Clear/almost clear with ≥2-grade improvement:
    - Tofacitinib 68%
    - Vehicle control 13% (p <0.001)

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### Dupilumab for atopic dermatitis

- Human monoclonal Ab against IL-4 receptor α subunit
  - Blocks IL-4 and IL-13 signaling important to Th2-mediated inflammation
- RCT in 109 adults with moderate-severe AD
  - EASI decrease of 50% & 75% after 12 weeks:
    - Dupilumab 85% & 62%
    - Placebo 35% & 15% (p <0.001)
  - More skin infections with placebo (24%) than drug (5%)