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

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Which of the following is the most likely diagnosis?

A  Acute hemorrhagic edema of infancy
B  Erythema multiforme
C  Kawasaki disease
D  Serum sickness
E  Urticaria
Transient lesions
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%)

Konstantinou et al Ped All Immunol 2011
Ricci et al JEADV 2010
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 runs rampant
- Useful in interactions with colleagues convinced it is erythema multiforme

Shah et al Pediatrics 2007
Mortureux et al Arch Derm 1998
Legrain et al Ped Derm 1990
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’

- Acute hemorrhagic edema of infancy
  - Facial/acral edema + fever + annular, but lesions are *fixed* and *purpuric*
Differential diagnosis of urticaria ‘multiforme’

- Erythema multiforme
  - Smaller, fixed lesions – last several days or longer
  - Central dusky skin that may lead to blistering/erosion, **NOT** clearing
  - Oral erosions common
  - Usually no facial/acral edema
EM DDx: don’t forget coxsackie A6!
Lesions *around* > inside mouth
CVA6 in 2 brothers: what a difference some eczema makes

‘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

• Tx: penicillin, ceftriaxone, doxycycline

Crews et al JAMA Pediatr 2014
EM-like “id” reaction to molluscum
‘BOTE’ sign for molluscum

Beginning
Of
The
End

Butala et al Pediatrics 2013
Differential diagnosis of urticaria ‘multiforme’

• Kawasaki disease
  – Facial/acral edema, polymorphic eruption can be urticarial or EM-like
  – 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 area involvement
  - Median onset day 8 (range, 4-54 days)
  - Duration 2-18 months

Haddock et al JAAD 2016
Kishimoto et al Acta Pediatr 2010
Garty et al Pediatr Derm 2001
New AHA Guidelines: evaluation of incomplete Kawasaki disease

McCrindle et al Circulation 2017 https://doi.org/10.1161/CIRC.0000000000000484
Differential diagnosis of urticaria ‘multiforme’

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

Tolpinrud et al JAAD 2011
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 **DERMATOGRAPHISM**!
  - Consider **cold** urticaria

- **Chronic ‘spontaneous’ urticaria**
  - Classic definition: regularly ≥6 weeks
  - Prevalence of 0.2-0.7%

*Bruske et al Ped All Immunol 2014; Lee et al Allergy Asthma Immunol Res 2017*
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 assay, basophil activation test (or autologous serum skin test)
  - ?? *H. pylori* or asymptomatic UTI in subset
  - Consider parasites, esp. if residence in/travel to endemic locations
  - *Food allergies are rarely the cause* (but often suspected by parents)

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Yilmaz et al Allergy Asthma Proc 2017
Chansakulporn et al JAAD 2014
Tolpinrud et al JAAD 2011
Chronic ‘spontaneous’ urticaria in children: associated findings

- Other autoimmune conditions
  - Thyroid autoAb in ~5-10%, compared to ~1% in general pediatrics population (vs 15-25% and 5-10% for adults)
  - Celiac disease in ~5%, compared to 0.5-1% in controls

- Psychiatric conditions
  - ~70%, compared to 30% in controls
  - Anxiety disorders most common

Levy Y et al Arch Dis Child 2003
Caminiti L et al Ped All Immunol 2005
Herguner S et al Br J Dermatol 2011
Kolkher et al Allergy 2017
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 or joint symptoms
Urticaria in children

AVOID undertreatment and oversedation!
Urticaria in children: treatment

- First-line: scheduled low-sedating, long-acting H1 antihistamine(s)
  - Often need more than standard dose ± >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]
  - IVIg
  - **AVOID prednisone**

Mitchell et al Int J Derm 2014
Bernstein et al J All Clin Immunol 2014
Remember 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/periocular involvement
  - Be hospitalized

Sugerman et al. Pediatr Derm 2011
Perianal and vulvovaginal (perineal) streptococcal infection

- Favors children ages 2-7 y
  - Boys > girls for perianal
- Sharply demarcated, bright red erythema
  - Pruritus, irritation, painful defecation/urination
  - Blood-streaked stools, vaginal discharge, fissures
  - Often also + throat cx for GAS
- Can trigger guttate psoriasis
- Tx: amoxicillin or 1\textsuperscript{st}/2\textsuperscript{nd} gen cephalosporin
  - Cefuroxime more effective than penicillin in one RTC

Clegg et al J Ped 2015
Cohen et al J Infect Dis 2015
Meury J Ped 2008
Streptococcal intertrigo

• Underrecognized cause of intertriginous eruptions in infants and toddlers
  – Sharply demarcated, intensely red
  – No satellite lesions
  – Foul odor

• Fever and bacteremia can occur

Chiriac et al J Ped 2017
Lopez-Corominas V et al Ped Derm 2015
Honig et al Pediatrics 2003
Neri et al Pediatr Dermatol 2007
“Psoriasiform id reaction”

- Initial diaper/intertriginous rash with ‘double hit’, e.g. sebopsoriasis + candidal or bacterial (e.g. streptococcal) infection
- This triggers a sudden, more widespread eruption of small pink, scaly psoriasiform papules
Infantile sebopsoriasis / psoriasis

Childhood psoriasis
Systemic treatment of pediatric psoriasis

- Moderate to severe disease
  - Not responsive to or intolerant of topical therapy
  - Impacting quality of life
- International retrospective study (n=390; 1990-2014)
  - Adverse events more frequent with methotrexate than TNF-inhibitors

Bronkners et al JAMA Derm 2017
Systemic treatment of pediatric psoriasis

• Current FDA-approved biologic options
  – Etanercept (11/2016 for age ≥4 y)
  – Adalimumab (*other indications age ≥2 y*)
  – Ustekinumab (11/2017 for age ≥12 y)

• Future possibilities
  – Adalimumab approval for peds psoriasis
  – Ongoing trial of ustekinumab in ages <12 y
  – Ongoing trial of ixekizumab and apremilast in children
  – Planned trials for other Th17/IL-23 inhibitors
  – Consideration of IL-22 as target

Bronkners et al JAMA Derm 2017
Etanercept for pediatric psoriasis

- Initial RTC in ages 4-17 y (n=211)
  - 0.8 mg/kg/week (max 50 mg)
  - PASI 75: 57% at 12 wks, 68% at 36 wks
  - No significant safety issues

- Open-label 5-year extension (n=69)
  - No malignancies, opportunistic infections

Paller et al JAAD 2016
Adalimumab vs methotrexate for pediatric psoriasis

- RTC in ages 4-17 y (n=211; 36% overweight/obese)
  - Adalimumab 0.8 mg/kg/QOwk (max 40 mg) or MTX 0.1-0.4 mg/kg/wk (max 25 mg)
  - PASI 75
    - Adalimumab: 58% at 16 wks
    - MTX: 32% at 16 wks (p = 0.03)
  - No significant safety issues

Papp et al Lancet 2017
Psoriasis and psoriasiform eruptions triggered by TNF inhibitors

- Favors scalp (~50%), posterior auricular area, face, umbilicus and extremities
- Also palmoplantar and flexural pustular eruptions
- Especially in patients with inflammatory bowel disease (~10%)
  - Mean onset 10-20 mos (range, <1 mo - >5 y) after starting anti-TNF therapy
- Unopposed interferon production and/or Th17 signaling

Eickstaedt et al Ped Derm 2017
Sherlock et al J Ped Gastr Nutr 2015
Perman et al Ped Derm 2012
Ustekinumab for adolescent psoriasis

• RTC in ages 12-17 y (n=110)
  – Ustekinumab 0.75 mg/kg [≤60 kg], 45 mg [>60-100 kg] or 90 mg [>100 kg] weeks 0 & 4 then Q12wks; vs half-dose and placebo
  – PASI 75: 80% at 12 weeks
  – PASI 90: 61% at 12 weeks (vs <30% in etanercept trial)
  – No significant safety issues

Good choice if *CARD14* mutation

– Plaque or pustular/erythrodermic psoriasis; also familial PRP
– Increased IL-23 → Th17

Landells et al JAAD 2015
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, precedes 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