Bugs and Drugs: What’s New in Hypersensitivity Reactions?

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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Soo6 - Treating Severe Skin Disease in Children
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DISCLOSURES

Zosano Pharma, Consultant, Honoraria
Rodan + Fields, Advisory Board, Honoraria
Causes of SJS/TEN in Kids

- Retrospective study of kids with SJS/TEN at Sick Kids and Children’s Hospital Boston between 2000-2007
- 55 cases: SJS 47, TEN 5, SJS/TEN 3

Mycoplasma Induced Rash and Mucositis Systematic Review

• Epidemiology
  – Young (mean 11.9 years)
  – Male (66%)

• Morphology
  – Mucosal predominant
  – Mild skin involvement

• Outcomes
  – Pigmentary alteration 6%
  – Mucosal complications 8%
  – Recurrence in 8%
  – Mortality 3% (all in 1940s – pre-antibiotics)

Outbreak of Mp-Associated SJS

- Outbreak of SJS at Children’s Hospital Colorado
- Mp associated SJS cases significantly more likely to have
  - Pneumonia
  - Preceding respiratory sx
  - ESR ≥ 35
  - ≤ 3 affected skin sites (“severity of skin was overall mild”)
- Treatments and length of stay were similar (mucosal dz was severe).

MIRM Diagnostic Criteria

- <10% BSA detachment*
- ≤ 2 mucosal sites
- Few atypical targets
- Evidence of atypical pneumonia (clinical and laboratory)

*Rare cases can have more BSA detachment, or no rash.
+ Age Criteria (3-18yrs?, 5-21yrs?)

How good are our tests for Mycoplasma pneumoniae?

- IgM/IgG
  - Specificity 25-100%
  - Sensitivity 52-100%

- IgA?
  - Titers rise earlier than IgM.

- PCR – respiratory (nasal wash or BAL), bulla fluid, skin bx
  - Very sensitive
  - Can shed bacteria for 4 months in OP
  - Not easily available at all hospitals

Mycoplasma + Skin

- Skin findings in up to 33% of Mp infections
- Wide range of cutaneous findings
  - Exanthema (8-33% of Mp infections)
  - Erythema nodosum
  - Urticaria
  - Stevens–Johnson syndrome (1-5% of Mp infections)

On your DDx: CIRM

*Chlamydia pneumoniae induced rash and mucositis*

- 21 cases of mucositis/rash associated with CP reported
- Very similar to MIRM
- Young, preceding URI
- Dx with PCR or Ig’s
- Treat with azithromycin

Pediatric Work-Up

- Mycoplasma IgM, IgG, IgA
- Mycoplasma PCR
- HSV IgM, IgG
- CXR
- Drug Chart

- Skin Biopsy – H&E, DIF
- Consider:
  - Viral PCRs
  - IIF
  - ESR
  - Others based on ddx
MIRM: Treatment

• Treat pulmonary infection with azithromycin

• Supportive care

• Other interventions:
  – Steroids? after infection treated → shorter LOS?
  – Cyclosporine?
  – IVIG? Rarely. If skin progresses to >10% BSA.
  – Amniotic membrane for eyes if severe.

SJS/TEN Medication Triggers

- Antiepileptics
  - Phenobarbital
  - Carbamazepine
  - Lamotrigine
  - Valproic acid
- Antibiotics
  - Sulfonamides
- NSAIDS
- Paracetamol/Acetominophen

Meta-analysis and individual patient data analysis of 3248 patients

Statistically significant benefit of corticosteroids in 1 of 3 analyses.

Steroids?

- In children with SJS do systemic steroids reduce morbidity or mortality?
  - Few quality studies

- Steroids may
  - Shorten fever duration & increase complication rate

- Occasionally use in SJS with evidence of ongoing inflammation

- Use 1-2mg/kg/day x ~5 days

- Caution in kids with behavioral or psych diagnoses

IVIG?

“IVIG cannot be recommended for SJS/TEN”


Huang et al. *BJD.* 2012. 167; 424-432.
IVIG treated group: Children vs. Adults

Children treated with IVIG do better than adults treated with IVIG.

Huang et al. BJD. 2012. 167; 424-432.
Our approach to IVIG

- Use it in TEN and SJS/TEN overlap
- Use high dose 4 g/kg total (1 g/kg/day x 4 days)
- Occasionally use in combination with steroids

*Children have lower risk of side effects from IVIG (thromboembolic and renal)*
Cyclosporine

Predicted mortality vs. observed mortality

- 4 studies (few children)
  - 2 retrospective
  - 2 prospective open

- Different CSA protocols
  - 3mg/k x 7 days
  - 3, 2, 1 mg/k x 10 d each

- Reduction in observed deaths compared with deaths predicted by SCORTEN

CSA: Pediatric Data

• 3 children treated with CSA for MIRM, SJS, SJS/TEN
  – Dose – 3mg/kg/day div BID (x 7-21 days)
  – Time to response 2.2 days (1.5-3 days)
  – Well tolerated

Outcomes of SJS/TEN Spectrum

- Mortality is very low in children (0.3-1.5%)*
- More meaningful outcome measures:
  - Complications
  - Time to remission
  - Length of hospital stay (7-9 days)*
  - Scarring (ocular, genital, oral, cutaneous)

SJS Spectrum: Recurrence

- Pediatrics 2011 - 18% recurrence (children only)
  - Not always the same trigger
- MIRM JAAD 2014 – 8% recurrence
- JAMA 2014 - 7% recurrence risk
  - Higher risk if: younger, male, rural, academic hospital

Recurrent SJS/TEN

• Genetic predisposition likely

• Important part of our patients’ health history
  – Life threatening allergy
  – Risk of another similar reaction (not necessarily to a related trigger)

11 yo girl w/sore throat, malaise, low grade fever, lymphadenopathy and a rash for 3 days. Taking minocycline for the last 4 weeks for periorificial dermatitis. LFTs are elevated.
Does she have a drug reaction or a viral syndrome?
Does she have a drug reaction or a viral syndrome?

Both
DIHS = Drug induced hypersensitivity syndrome = DRESS = Drug Reaction with Eosinophilia and Systemic Signs
DIHS/DRESS

- Polymorphic rash, facial edema, LAD
- Systemic symptoms (pharyngitis, fever)
- Abnormal labs:
  - ↑eos (40%), LFTs (80%), Cr (40%)
- Meds:
  - Anticonvulsants
  - Antibiotics
  - Sulfonamides
  - Allopurinol
- Abnormal drug metabolism (HLA associations)
- Starts 1-6 weeks after drug initiation

Role of Viruses in DIHS

• Viral reactivation (HHV-6, EBV, HHV-7, CMV): 30-80% patients
  – Viral reactivation and visceral infection are associated with DRESS
  – Viral antibody titers and viral load correlate with severity, duration

• Viral studies do not become positive immediately, can rise over weeks
  – Check HHV-6, HHV-7, EBV, CMV antibody titers and viral loads weekly

Does virus type correlate with morphology?

- Restrospective study of Japanese patients (N=62) with DIHS, SJS, SJS/TEN, TEN
- Followed viral studies over 2 years
- DIHS – HHV-6 elevated in acute phase
- SJS – EBV in acute phase and after resolution
DIHS Treatment

• must d/c med
  – list med as an allergy

• systemic steroids for weeks to months
  – start at 1-2 mg/kg/day
  – additional immunosuppression if unable to taper steroids

• follow labs carefully as you taper

• Antiviral therapy may be helpful in addition to corticosteroids
  – Gancyclovir – HHV-6 and CMV

Is this child allergic to amoxicillin?
Aminopenicillin + EBV = Rash?

• Old studies:
  – 69-100% got rash
  – RR of rash = 5.5-11
  → Not a true allergy, reversible

• New studies:
  – 13-30% got rash
  – RR of rash = 0.58-1
  → Unclear if allergy or not.
Allergy vs. transient immunostimulation?

- Patients with confirmed EBV infection + rash when given amoxicillin
  - Tested for allergy with specific IgE, prick tests, patch tests
  - 5 of 8 had positive Amox patch tests, 1 positive oral challenge, 4 refused challenge
  - 2 also positive patch to PCN
  - all negative for Cephalosporins

Jappe U. Allergy. 2007 Dec;62(12):1474-5
Amox rash – bottom line

• Most common with EBV, but other viruses implicated
• Likely 2 populations:
  1. Transient EBV associated loss of immune tolerance (most people)
  2. True, persistent delayed-type hypersensitivity.
• Consider testing/referring to allergy (but know that the tests aren’t perfect)
Bugs and Drugs

- Drugs and infections interact with the immune system and the skin in fascinating and complex ways.
  - MIRM - distinct morphology, epidemiology
  - SJS/TEN – kids do better, consider CSA
  - Complex drug reactions - look for viral infections
Thank you

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