S038- Treating Severe Skin Disease in Children

Management of Severe Hypersensitivity Reactions in Children

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Session S038:
Treating Severe Skin Disease in Children

DISCLOSURES
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Objectives

- Diagnose severe hypersensitivity disorders in children
- Utilize laboratory testing to diagnose hypersensitivity disorders
- Treat hypersensitivity disorders in the pediatric population
Case
3-year-old boy with Down syndrome

- Spreading erythema x 3 days
- Started as “diaper rash”
- Eye swelling x 1 day
- Afebrile
- Noisy breathing
- O2 saturation 90%
- Hemorrhagic conjunctival injection
- Buccal mucosa and lip erosions
Toxic Epidermal Necrolysis (TEN)

- Trimethoprim–sulfamethoxazole x 3 doses for MRSA external ear infection

- Trimethoprim–sulfamethoxazole discontinued immediately on presentation
Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

- Clinical findings
  - Erythematous macules
  - Bullae/vesicles
  - Nikolsky sign
    - Detachment of epidermis with lateral pressure
  - Asboe-Hansen sign
    - Extension of a blister to adjacent unblistered skin when pressure is put on the top of the bulla
  - Involvement of 2 mucous membranes
  - Skin pain
  - Prodromal symptoms: fever, malaise, vomiting
Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

- **SJS-TEN Spectrum:**
  - SJS <10% BSA
  - SJS-TEN overlap 10-30% BSA
  - TEN >30% BSA

- Usually occurs 7-21 days after the inciting drug was started

- Mortality overall: 25-50% in TEN; 5% in SJS
- Mortality in children: 0.3-1.5%

Bologna 3rd Ed.
Differential Diagnosis
Staphylococcal Scalded Skin Syndrome
Erythema multiforme
Mycoplasma Induced Rash and Myositis (MIRM)
Hand Foot Mouth Disease
“Eczema coxsackium”
Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

- 1.2 – 6 per million (SJS)
- 0.4 – 1.2 per million (TEN)

Risk factors
- HIV
- Lymphoma
- Slow acetylator genotypes
- HLA-B*1502: Asians and East Indians exposed to carbamazepine
- HLA-B*5801: Han Chinese exposed to allopurinol
- HLA-A*3101: Europeans exposed to carbamazepine
Medications most frequently associated with TEN/SJS

- Allopurinol
- Aminopenicillins
- Antiretroviral drugs, especially NNRTIs
- Barbiturates
- Carbamazepine
- Phenytoin anticonvulsants
- Lamotrigine
- Piroxicam
- Sulfadoxine
- Sulfasalazine
- Trimethoprim–sulfamethoxazole
Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

Treatment

– Stop the offending agent quickly!
  • Difference in mortality if stopped at first sign of blister/erosion
    – 11% mortality for early discontinuation vs. 27% for late discontinuation
      (with short half-life drugs, $t_{1/2} < 24$ hours)

– Supportive care
  • ICU care; consider transfer to regional burn center
  • Generous emollient use
  • Avoid manipulation
  • Infection prevention
  • Ophthalmology consultation
  • Urology consultation
  • Pulmonary toilet
  • Mouth care
  • Oral antacids

Stevens Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN)

Treatment

- Low prevalence of SJS/TEN limits controlled, prospective clinical trials

- Treatments reported to be helpful in case series or case reports
  - cyclosporine (3–4 mg/kg/day)
  - cyclophosphamide (100–300 mg/day)
  - Plasmapheresis
  - N-acetylcysteine (2 g/6 h)
  - TNF-α antagonists (e.g. etanercept, infliximab)

- Systemic glucocorticoids

- Intravenous immunoglobulins (IVIg): 8 of 11 studies (each with at least 10 patients) suggest that IVIg (at a total dose of >2 g/kg administered over 3 - 4 days) may reduce TEN associated mortality
  - Our patient: treated with IVIg 1 gram/kg/day for 3 days (total cumulative dose 3 grams/kg)
Glucocorticoids

Meta-analysis: 27 studies, 1209 patients

IVIG

Meta-analysis:
27 studies, 1209 patients

IVIG in SJS/TEN
Meta-analysis: 17 studies

Biologic TNFα inhibitors in SJS/TEN

- TNFα is increased in serum and blister fluid in SJS/TEN

- Systematic review:
  - 2 randomized control trials
  - 4 case series
  - 21 case reports
  - Total 91 patients
    - 24 treated with infliximab
    - 67 treated with etanercept
  - TNFα inhibitor used as:
    - monotherapy, second-line treatment, combination therapy
  - 79 patients (87%) responded favorably

## Pediatric Cases: TNFα inhibitors in SJS/TEN

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Comorbidities</th>
<th>Dx</th>
<th>Treatment</th>
<th>Response</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>17y/F</td>
<td>None</td>
<td>TEN</td>
<td>- Dexamethasone + IVIG (0.1 g/kg) x 2 days (failed)</td>
<td>No new bullae within 24 hours</td>
<td>- Post-inflammatory hyperpigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- IVIG (0.4 g/kg) x 4 days + dexamethasone steroid taper (failed)</td>
<td></td>
<td>- Pseudomembranous conjunctivitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- infliximab 5 mg/kg x 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17y/F</td>
<td>Epilepsy</td>
<td>TEN</td>
<td>- IVIG 2 g/kg/d x 1 day (failed)</td>
<td>No new bullae within 24 hours</td>
<td>- Bacteremia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- infliximab 5 mg/kg: day 2, day 8</td>
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<tr>
<td>7y/M</td>
<td>Epilepsy, Autism</td>
<td>TEN</td>
<td>- IVIG 2 mg/kg/day x 1 day (failed)</td>
<td>Disease progression stopped &lt; 24 hours</td>
<td>- None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- infliximab 5 mg/kg x 1</td>
<td></td>
<td></td>
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<tr>
<td>11y/F</td>
<td>None</td>
<td>TEN</td>
<td>- Prednisolone 2 mg/kg IV x 2 d + IVIG 0.6 mg/kg x 6 days (failed)</td>
<td>Nearly healed in 2 weeks; alive</td>
<td>- Corneal neovascularization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- infliximab 250 mg x 1 dose</td>
<td></td>
<td>- Keloidal scarring</td>
</tr>
<tr>
<td>11y/F</td>
<td>None</td>
<td>SJS/TEN</td>
<td>- methylprednisolone x 4 days (failed)</td>
<td>Disease progression stopped; alive</td>
<td>- None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Methylprednisolone + cyclosporine 5 mg/kg/day x 3 days (failed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- etanercept 25 mg x 2 daily doses</td>
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</table>

Case
12-year-old boy

- 6 day history of oral ulceration
- Cough and fever 1 week prior (Tmax 103 F)
- No preceding prescription or over the counter medications
- No skin lesions
- No improvement with 2 days of oral acyclovir (presumed herpes gingivostomatitis)
- Transferred for concern for SJS
ROS:
- Photophobia
- Epistaxis
- Dysphagia
- Dysuria

Labs:
- UA: blood 2+, urine RBCs 2150
- Mycoplasma IgG 4349 (>320)/IgM 1432 (>950 is positive)
- HSV PCR- negative
- Chlamydia/GC PCR- negative
- Chest x-ray- within normal limits
Mycoplasma Induced Rash and Mucositis (MIRM)

- **Clinical presentation**
  - Prodrome: cough, fever, malaise x 1 week
  - Prominent mucositis, usually involves 2+ sites
  - Purpuric macules, vesicles, atypical target lesions
    - Less likely to be only acral in distribution
  - Skin lesions may be absent in ~ one-third of cases: “MIRM sine rash”

- More common in winter
- More common among children and adolescents (Boys > Girls)
  - Mean age 11.9 +/- 8.8 years
  - Males (66%)

Mycoplasma Induced Rash and Myositis (MIRM)

- 17-year-old boy
- Typical targets on trunk
- Mucositis
  - Conjunctiva
  - Lips, oral mucosa
  - Penile mucosa
- History of cough and low grade fever x 1 week
- 2 prior similar episodes
- ALL: Trimethoprim-sulfamethoxazole (SJS)
16-year-old girl

- Cough, low grade fever x 1 week
- Dysuria
- Vaginal discharge
- Mucositis:
  - Conjunctiva
  - Lips and Oral mucosa
  - Vulva

UA: 2+ blood, 21-50 RBCs
Urine culture: neg
Mycoplasma IgM: positive
Mycoplasma IgG: + 0.63 (neg<0.09)
GC/CT PCR: negative
HSV IgG: negative
Mycoplasma Induced Rash and Mucositis (MIRM)

Clinical features help *distinguish* from drug-induced SJS/TEN and herpes-related Erythema Multiforme

- Predominant mucosal disease
- Relatively sparse cutaneous disease
- Young age of onset
Mycoplasma Induced Rash and Mucositis (MIRM)

Compared to non-mycoplasma induced erythema multiforme

- Longer hospital length of stay (9.5 days) than non-mycoplasma induced Erythema Multiforme (5.1 days)

- Increased risk of mucosal sequelae
  - Ocular
    - Conjunctival adhesions
    - Corneal scars
    - Tarsus fibrosis
  - Genital
    - Phimosis
    - Vulvar adhesions


Mycoplasma associated mucositis (MIRM)
- Full thickness epidermal necrosis and separation
- Pauci-inflammatory
- “TEN-Like” 14/14 (100%)
- Mycoplasma pneumoniae PCR negative

Non-mycoplasma associated erythema multiforme
- Interface dermatitis
- Superficial and deep perivascular infiltrate with lymphocytes and eosinophils
- TEN like in 10/27 biopsies (48%)

Other triggers: Chlamydia pneumoniae (CP)

- 21 cases of CP induced rash and mucositis
- Preceding cough, congestion
- Diagnostic tests
  - PCR
  - Serologies
- Treatment: azithromycin
Treatment: MIRM

- Currently no evidence-based guidelines
- Antibiotics (macrolides)
- Systemic glucocorticoids
- IVIG
- Supportive and symptomatic care
- Dermatology, ophthalmology, and urology/gynecology consult to prevent long term sequelae of mucocutaneous lesions
16 year-old girl with history of ALL and refractory seizure disorder

- Skin eruption x 2 days
- Fever 38.4 °C (101 °F)
- Non-productive cough
- Cervical lymphadenopathy
- Facial and hand edema
Medication History

- Divalproex sodium (depakote)
  - 5 weeks before rash
- Added lamotrigine (lamictal)
  - 4 weeks before rash

Labs

- Eosinophils 12%
- AST 118
- ALT 74
- Free T4 0.68 (0.8 - 1.8 ng/L), TSH within normal limits
- Cr within normal limits
- UA within normal limits
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Syndrome (DIHS)

- Manifests **2 to 6 weeks** after the initiation of offending drug
- **10% Mortality rate**

- Fever
- Skin eruption
  - most often morbiliform
- Lymphadenopathy
- Edema of face and hands

- Eosinophilia
- Atypical lymphocytosis
- Hepatitis/Transaminitis- up to 50%
- Pulmonary infiltrates
- Nephritis
- Myocarditis
Mucosal involvement in DRESS

• Estimated to occur in 50% of DRESS cases
• *Milder* than TEN/SJS spectrum
  – Conjunctival injection
  – Mild mucosal ulcerations

Mucosal involvement in DRESS
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Evaluation

- CBC/diff
- Liver function tests
- Creatinine
- Urinalysis
- Baseline thyroid function studies

Treatment

- Discontinue offending medication!
- Oral corticosteroids with 3-6 week taper if reaction severe
- Monitoring
  - Thyroid function tests- 2 to 3 months after
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Common Culprit Medications

<table>
<thead>
<tr>
<th>Aromatic Anticonvulsants</th>
<th>Antibiotics</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Sulfonamides</td>
<td>Terbinafine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Minocycline</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Nitrofurantoin</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Lamotrigine</td>
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<td></td>
</tr>
</tbody>
</table>
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Cross reactivity between anticonvulsant medications may be as high as 75%
- If DRESS occurs with aromatic anticonvulsant, *avoid* the other aromatic anticonvulsants

| Phenytoin (Dilantin) | Carbamazepine (Tegretol) | Phenobarbitone (Phenobarbital) | Lamotrigine (Lamictal) |
- Started divalproex sodium (depakote) - 5 weeks before rash
- Added lamotrigine (lamictal) - 4 weeks before rash
Anticonvulsant hypersensitivity syndrome/DRESS

- Among patients taking lamotrigine:
  - Rate of serious rashes - 0.1%

- Of patients with anticonvulsant hypersensitivity (DRESS) syndrome to lamotrigine, 60% also taking valproic acid derivative
  - Co-administration of valproic acid derivative triples the half-life of lamotrigene


Serious Rash
serious rashes requiring hospitalization and D/C tx incl. Stevens-Johnson syndrome, rare cases of toxic epidermal necrolysis, and rash-related deaths; incidence w/ adjunctive epilepsy tx 0.8% in 2-16 yo and 0.3% in adults; bipolar and other mood disorder incidence 0.08% as initial monotherapy and 0.13% as adjunctive tx; age is only risk factor identified as predictive for risk of rash occurrence or severity; other risk factors may incl. concurrent valproic acid derivative or exceeding initial lamotrigene dose or dose escalation recommendations; most life-threatening rashes occur in the first 2-8wk of tx w/ isolated cases after prolonged tx; though benign rashes may also occur D/C tx at 1st sign of rash unless clearly not drug related; D/C tx may not prevent rash from becoming life-threatening or permanently disabling or disfiguring

Black Box warning
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Associated with reactivation of human herpesvirus (HHV)
  - HHV 6
  - HHV 7

- HHV 6 positive DRESS is associated with a more severe course and longer hospital length of stay (LOS)
  - LOS (11.5 days vs. 5 days, $P = 0.039$)
  - Number of febrile days (12.5 days vs. 3 days, $P = 0.032$)

Hara H, et al. Dermatology 2005; 211:159-161
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Reported autoimmune sequelae
  - Autoimmune thyroiditis
  - Type 1 diabetes mellitus
  - Vitiligo
  - Alopecia areata
  - Systemic lupus erythematosus

- In a study of 145 adult patients with DRESS/DIHS, the most common autoimmune sequelae were
  - Autoimmune thyroiditis (4.8%)
  - Type 1 diabetes mellitus (3.4%), sometimes fulminant within 1-2 months

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary

- **Serious drug reaction**
  - 10% mortality

- **Clinical presentation**
  - Fever
  - Lymphadenopathy
  - Facial/hand swelling
  - Erythematous skin eruption
  - May have mild mucosal involvement
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Summary

- In acute phase, may affect multiple organ systems
  - Liver
  - Lungs
  - Kidneys
  - Heart

- In subacute phase (~2-3 months after resolution), may affect
  - Thyroid

- Risk of autoimmune sequelae
THANK YOU