Big rashes in little patients:

Severe drug eruptions and cutaneous infections

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Disclosures

- No relevant relationships with industry
- Discussion of off label medications
Learning Objectives

• Recognize severe drug eruptions in children
• Discuss treatment options
• Diagnose cutaneous infections in young children
Case # 1

An 8 year old girl is evaluated because of a 4 day history of worsening generalized skin eruption and fever. Physical exam reveals generalized lymphadenopathy. Hepatic transaminase levels are twice the upper limit of normal. Which of the following drugs is the most likely cause?

A. Valproic Acid
B. Trimethoprim- Sulfamethoxazole
C. Methylphenidate
D. Prednisone
E. Cephalexin
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DHS/DRESS Reaction

- Drug Reaction with Eosinophilia and Systemic Symptoms
- Other terms: Drug Hypersensitivity Syndrome (DHS) or Drug Induced Hypersensitivity Syndrome (DIHS)
- Can be mistaken for:
  - Viral infections with fever and rash
  - Kawasaki disease in young children
  - Lymphoma
  - Hemophagocytic lymphohistiocytosis (HLH)
  - Amoxicillin/EBV reaction
  - Measles
  - SJS/TEN
# DRESS Diagnostic Criteria:

<table>
<thead>
<tr>
<th>European (RegiSCAR)</th>
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<tbody>
<tr>
<td>Reaction suspected to be drug related</td>
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<tr>
<td>Acute rash</td>
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<tr>
<td>Hospitalization</td>
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<tr>
<td>Fever &gt; 38°C</td>
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<tr>
<td>Enlarged lymph nodes ≥ 2 sites</td>
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<tr>
<td>Involvement of ≥ 1 internal organ</td>
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<td>Blood count abnormalities</td>
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<td>Lymphocytes above or below normal limits</td>
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Summary of criteria for DRESS

**Skin eruption**
- morbilliform, deep red to purple
- vasculitis has been described

**Clinical signs**
- onset 2-6 weeks after drug started
- fever > 38 C
- face and hand edema
- lymphadenopathy
- interstitial pneumonia, nephritis or carditis, hepatitis
- late onset autoimmune hypothyroidism

**Lab criteria**
- eosinophils > 1500 (present in 60% of patients)
- atypical lymphocytosis (in 50% of patients)
- elevated liver enzymes
- viral reactivation: HHV6, HHV7, EBV, CMV
Index of Suspicion

Most DHS/DRESS reactions are caused by these medications:

- Anticonvulsants
  - Aromatic: Phenobarbital/Phenytoin/Carbamazepine (cross react)
  - Carbamazepine most common in children
  - Lamotrigine and Zonisamide
- Antibiotics: Minocycline, Dapsone
- HIV medications: Abacavir, Nevirapine, Raltegravir
- Sulfa medications: Sulfamethoxasole, Sulfasalazine
- Other: NSAIDs, Allopurinol, Captopril, Azathioprine
- Genetic predisposition with certain HLA types
- Some are idiosyncratic reaction to drugs with concurrent viral infection
- May have viral reactivation: HHV6, HHV7, EBV, CMV
## Drugs associated with specific internal risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk</th>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>Renal</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Renal</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Hepatic and Renal</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Hepatic, Pulmonary, Cardiac</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

Husain Z, DRESS Syndrome, JAAD May 2013
DRESS- differential diagnosis

A few examples of conditions on the differential:
Fever for >5 days and Rash

- did not respond to IVIG treatment for Kawasaki disease
- negative infectious workup
- persistent fever
- anemia and hepatosplenomegaly
- elevated triglycerides and ferritin
- bone marrow biopsy done
HLH: Hemophagocytic Lymphohistiocytosis

- Fever (>7 days), Hepatosplenomegaly, Cytopenias
- Low fibrinogen, High triglycerides, Ferritin>500
- Skin changes in 25%
  - morbilliform
  - purpuric/petechial
- Hemophagocytosis on bone marrow biopsy- not visible on skin biopsy
- Etiology:
  - EBV reactivation
  - Mutations: STX11, PRF1, RAB27A, STXBP2
• Fever and rash with pinpoint pustules
• 2 weeks prior
  • amoxicillin- clavulanate

photo courtesy Dr. Carol Cheng
AGEP: Acute Generalized Exanthematous Pustulosis

- Fever, non follicular pustules, often unwell
- Appears within 1-4 days of drug administration
- Lasts 1-2 weeks, then resolves
- Desquamation
- Some children with variants in gene encoding IL-36 receptor antagonist
- More common in adults
- DDx includes pustular psoriasis
AGEP: Acute Generalized Exanthematous Pustulosis

Causative Drugs:

- Beta lactam (most common), Macrolides
- Calcium channel blockers, antimalarials
- Carbamazepine, acetaminophin
- Other antimicrobials (terbinafine, isoniazid)

Therapy:

- Withdrawal of drug, treat symptomatically
DHS/DRESS Treatment

- Withdrawal of causative drug - this is usually NOT enough
- Systemic corticosteroids 1 mg/kg/day with *gradual* taper
- Supportive care
- Case reports of IVIG, plasmapheresis, Immunosuppressives (cyclosporine), anti viral meds
Infantile DRESS treated with steroid taper and ganciclovir

- 3 month old - phenytoin, phenobarbital, levetiracetam for seizures
- 4 weeks later- morbilliform rash, leukocytosis, eosinophilia, AST 2186, ALT 1070
- High CMV IgG and PCR, liver biopsy with CMV inclusions
- Treated with ganciclovir 5 mg/kg bid for 3 weeks
- Steroids were tapered
- Baby recovered and taken off liver transplant list
- Authors recommend checking HHV 6, HHV 7, CMV and EBV viral antibody titers and viral loads at 1-2 week intervals
  - ganciclovir covers HHV 6 and CMV
- Further studies needed to assess antiviral treatments in children with DRESS

Chow et al Use of antiviral medications in DRESS: a case of infantile DRESS. Pediatr Dermatol 2018
Case # 2

A 3 year old boy of Filipino descent is started on carbamazepine for his epilepsy and develops a bullous skin eruption. Which of the following lab abnormalities is most likely to be present?

• Deficiency of interleukin 1 receptor antagonist
• Decreased cytochrome b5
• Eosinophilia
• Presence of HLA-B*1502
• Presence of BP 180 Antigen
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• Presence of BP 180 Antigen
SJS and TEN Pharmacogenomics- genetic susceptibility to certain drugs

- Genetic polymorphisms of the human leukocyte antigens (HLA) and cytochromes P450 (CYP)

- **HLA*B15:02- carbamazepine causing SJS/TEN in Asians and South East Asians**

- **HLA*B58:01-Allopurinol causing SJS/TEN in Han Chinese**

- **HLA*A3101- Europeans exposed to carbamazepine**

- **HLA*B1201 - Dapsone, in Chinese and Thai populations**

- **Cytochrome P450: CYP2C polymorphism- risk of SJS from Phenytoin in Asian patients**

NEJM  2011;364-1126-1133
Pharmacogenet Genomics 2016 , 2017
Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

- Skin is painful, dusky
- Skin sloughing, and dead skin in center of lesions
- Children have fever
- SJS: less than 10% BSA and 2 mucous membranes
- SJS/TEN: 10-30% BSA
- TEN: greater than 30% BSA
  - eyes, nose, throat, lungs, esophagus, anus, urethra
- Time is skin: hours matter!!!
SJS/TEN etiology

MEDICATIONS:

- Anticonvulsants
  - Phenobarbital/Phenytoin/Carbamazepine (cross react)
  - Other: Lamotrigine, Zonisamide
- Antibiotics (many): Penicillins, Fluoroquinolones, Cephalosporins, Minocycline
- HIV medications: Nevirapine
- Sulfa medications: Sulfamethoxazole, Sulfasalazine
- Other: Allopurinol, Oxicam, NSAIDS, Azathioprine, Captopril….
SJS/TEN Treatment

Off label:

- IVIG, prednisonone, cyclosporine
- Supportive care essential
- ICU/Burn unit if significant BSA involvement
- Less mortality in children compared to adults
SJS/TEN, What’s New?
• 2.2 days for disease cessation, average 13 days for complete healing

• Proposed 3 mg/kg/day of cyclosporine IV divided bid for one week, followed by 1.5 mg/kg/day divided bid

• Monitoring CBC and CMP daily

• Trials needed to determine safety and efficacy in children
SJS/TEN TNF alpha blockade

- Case series of 10 patients treated with Etanercept
  - given single dose of 50 mg
  - 7-20 days until re-epithelialized
  - no deaths
- New Study: RCT of 96 patients comparing Etanercept and steroids
  - Etanercept decreased the SCORTEN-based predicted mortality rate (17% predicted, 8.3% observed)
  - Median time for skin healing was 14 days for Etanercept, 19 for steroids
- Also several case reports of pediatric patients treated with infliximab 5 mg/kg x 1

Wang CW et al J Clin Invest 2018
Wojtkiewicz et al Acta dermato-venerol 2008
Zarate-Correa et al J Inv Allerg& Clin Immunol 2013
TEN in an EB patient after BMT

• 3 year old with RDEB
• BMT for his EB treatment
• 16 days later- epidermal sloughing
• Biopsy consistent with TEN
• No other evidence of GVHD
• On multiple antibiotics
• Treated with IVIG and cyclosporine - survived

Boull et al Toxic epidermal necrolysis in Recessive Dystrophic Epidermolysis Bullosa after Bone Marrow transplantation J Pediatr 2016
Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: A systematic review

Theresa N. Canavan, MD, Erin F. Mathes, MD, Ilona Frieden, MD, and Kanade Shinkai, MD, PhD

Birmingham, Alabama, and San Francisco, California

• Reviewed 202 reported cases

• Atypical Stevens Johnson Syndrome or Erythema Multiforme

• Rename: *Mycoplasma-pneumoniae* Induced Rash and Mucositis (MIRM)
MIRM: Mycoplasma Induced Rash and Mucositis
Mycoplasma Induced Rash and Mucositis (MIRM)

- Predominant mucosal involvement
- Minimal cutaneous involvement
- Patients young (mean age 11.9 years)
- Male (66%)
- Treatment: no consensus
- Steroids, IVIG and supportive care
- Treating mycoplasma does not seem to alter course of skin disease

Canavan et al J Am Acad Dermatol 2015;72(2) 239-45
Case # 3
Diagnosis?

- Staphylococcal Scalded Skin Syndrome (SSSS)
Staphylococcal Scalded Skin Syndrome

• Staphylococcal toxin-mediated infection:
  • sometimes confused with TEN if extensive
  • bullae much more superficial
• Phage group II strains (types 3A, 3C, 55, 71)
• Exfoliative toxins cause bullae (ET-A and B)
  • target desmoglein 1
Why do you get SSSS?

- Immature or impaired renal function
- High Staphylococcus aureus burden
- Lack of antibodies to toxin
  - 91% of adults have anti toxin antibodies
  - Only 30% of babies have them
Staphylococcal Scalded Skin Syndrome

- Cultures from intact bullae are usually negative
- Culture all orifices:
  - S. aureus may be cultured from conjunctiva, nasopharynx, feces or pyogenic focus on skin
- Blood cultures usually negative in kids
SSSS Treatment

• Antibiotics: Penicillins, Cephalosporins, Clindamycin

• combination of penicillinase -resistant penicillin and clindamycin suggested as initial therapy until culture results available

• MRSA strain may produce toxin -treat with vancomycin or based on susceptibility

• Wound care

• Management of pain, temperature, fluids, nutrition

• neonates and infants are generally admitted

• Identify and treat S. aureus carriers

Braunstein et al Antibiotic sensitivity and resistance patterns in pediatric staphylococcal scalded skin syndrome Pediatr Dermatol 2014
Case # 4

- Healthy 2 year old girl
- Papulovesicular eruption x 2 days
Investigations

- Swab for PCR positive for VZV
- Child received varicella vaccine at 1 year of age
- Further testing revealed vaccine strain zoster virus
Pediatric vaccine-strain Herpes Zoster

- Pediatric zoster usually caused by natural infection with VZV
  - in utero infection or chicken pox in first two years
- Among vaccinated children up to half of cases can be due to vaccine strain VZV
- May correlate to site of vaccination
- Prognosis is excellent
  - unlike adults do not usually suffer sequelae
- Consider treatment with 7 day course of acyclovir

Conclusions

- DHS/DRESS syndrome can mimic other conditions
- Genetic basis to many severe drug reactions
- Mycoplasma and MIRM
- Chicken pox vaccine may cause zoster in young children