DRESS Syndrome
Not Your Typical Prom Attire

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Mayo Clinic Pharmacy Grand Rounds – Rochester, MN
June 5th, 2018
DRESS Syndrome

Drug Reaction with Eosinophilia and Systemic Symptoms
Objectives

• Describe clinical and laboratory findings of DRESS syndrome
• Differentiate DRESS syndrome from other adverse cutaneous reactions
• Recognize medications most likely to cause DRESS syndrome
• Select an appropriate treatment plan for a patient diagnosed with DRESS syndrome
Evolving Nomenclature

- Drug-induced pseudolymphoma
- Anti-convulsant hypersensitivity syndrome
- Drug-induced delayed multiorgan hypersensitivity syndrome
- Drug rash with eosinophilia and systemic symptoms
- Drug-induced hypersensitivity syndrome
- Hypersensitivity syndrome

Epidemiology

- Incidence not well-known
- Estimated risk 1 in 1000 to 1 in 10,000 drug exposures
- Mortality ~10%
  - Fulminant hepatic failure

Prospective RegiSCAR Study

• Observational multinational registry study
• Enrolled 201 patients
  • 117 cases probable or definite DRESS
• Define biological and clinical parameters
• Diagnostic scoring tool

SCAR = severe cutaneous adverse reactions
Clinical Manifestations

- Acute Skin Eruption
- Internal Organ Involvement
- Hematological Abnormalities
- Fever

2-6 weeks
Skin Eruption

Maculopapular Eruption

- 100% diagnoses
  - Polymorphic 85% diagnoses
  - Monomorphopic 15% diagnoses
- Variable clinical and temporal progression

Diffuse, confluent, and infiltrated erythema
Follicular accentuation

Skin Eruption

- >50% BSA
  - 79% diagnoses
- 68% diagnoses included two or more:
  - Facial edema
  - Infiltrated lesions
  - Scaling or desquamation
  - Purpura
- Pruritus
  - 81% diagnoses

BSA = body surface area

Skin Eruption
Skin Eruption
Hematological Abnormalities

- 100% diagnoses

<table>
<thead>
<tr>
<th>Type of Hematological Abnormality</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilia Grade 2 (≥1500 x 10⁹/L)</td>
<td>81%</td>
</tr>
<tr>
<td>Eosinophilia Grade 1 (700-1499 μL⁻¹)</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Leukocytosis (&gt;10,000 μL⁻¹)</td>
<td>95%</td>
</tr>
<tr>
<td>Neutrophilia (&gt;7000 μL⁻¹)</td>
<td>79%</td>
</tr>
<tr>
<td>Monocytosis (&gt;1000 μL⁻¹)</td>
<td>69%</td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>67%</td>
</tr>
<tr>
<td>Lymphocytosis (&gt;4000 μL⁻¹)</td>
<td>52%</td>
</tr>
<tr>
<td>Thrombocytosis (&gt;400000 μL⁻¹)</td>
<td>19%</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100000 μL⁻¹)</td>
<td>7%</td>
</tr>
</tbody>
</table>

Fever

- ≥38.0°C
  - 97% diagnoses
- ≥2 episodes of ≥38.0°C
  - 21% diagnoses

Internal Organ Involvement

- 91% diagnoses

<table>
<thead>
<tr>
<th>Number of Organs Involved</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>35%</td>
</tr>
<tr>
<td>≥3</td>
<td>20%</td>
</tr>
</tbody>
</table>
## Internal Organ Involvement

<table>
<thead>
<tr>
<th>Organ Involved</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>75%</td>
</tr>
<tr>
<td>Kidney</td>
<td>37%</td>
</tr>
<tr>
<td>Lung</td>
<td>32%</td>
</tr>
<tr>
<td>Spleen</td>
<td>15%</td>
</tr>
<tr>
<td>Muscle/Heart</td>
<td>13%</td>
</tr>
<tr>
<td>Gastrointestinal Tract</td>
<td>5%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>4%</td>
</tr>
<tr>
<td>Thyroid Gland</td>
<td>2%</td>
</tr>
</tbody>
</table>
Less Common Signs & Symptoms

• Lymphadenopathy
  • 54% diagnoses

• Mucosal involvement
  • 56% diagnoses

Mucosal Location % of Patients

<table>
<thead>
<tr>
<th>Mucosal Location</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth, throat, and lips</td>
<td>52%</td>
</tr>
<tr>
<td>Eyes</td>
<td>13%</td>
</tr>
<tr>
<td>Genitalia</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

Learning Assessment – Question 1

Which of the following are the most likely clinical manifestations of DRESS syndrome?

A. Acute skin eruption, hematological abnormalities, fever, and mucosal involvement

B. Acute skin eruption, hematological abnormalities, fever, and internal organ involvement

C. Acute skin eruption, hematological abnormalities, fever, and lymphadenopathy

D. Hematological abnormalities, fever, mucosal involvement, and lymphadenopathy
Learning Assessment – Question 1

Which of the following are the most likely clinical manifestations of DRESS syndrome?

A. Acute skin eruption, hematological abnormalities, fever, and mucosal involvement

B. Acute skin eruption, hematological abnormalities, fever, and internal organ involvement

C. Acute skin eruption, hematological abnormalities, fever, and lymphadenopathy

D. Hematological abnormalities, fever, mucosal involvement, and lymphadenopathy
Onset

Day 0
Exposure to Offending Drug

2-6 weeks
Typical Onset of DRESS Syndrome Signs and Symptoms
Median = 22 days
IQR = 17-31 days

6-13 weeks
Less Common Onset of DRESS Syndrome Signs and Symptoms

IQR = interquartile range

Clinical Course

Day 0 = onset of erythema

Horizontal bars = extreme values
Boxes = interquartile range
Vertical bars = median

Offending Agents

- **Anticonvulsants**: 35%
- **Allopurinol**: 20%
- **Sulfonamides**: 18%
- **Antibiotics**: 12%
- **Other Drugs**: 4%
- **Concomitant/Unknown/Non-exposure**: 11%

# Offending Agents

<table>
<thead>
<tr>
<th>Medication Category</th>
<th>Specific Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, valproic acid, zonisamide</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Amoxicillin, ampicillin, azithromycin, cefotaxime, dapsone, ethambutol, isoniazid, levofloxacin, linezolid, metronidazole, minocycline, piperacillin/tazobactam, pyrazinamide, quinine, rifampin, sulfasalazine, streptomycin, trimethoprim-sulfamethoxazole, vancomycin</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Abacavir, boceprevir, nevirapine, telaprevir, zalcitabine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Bupropion, fluoxetine</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Amlodipine, captopril</td>
</tr>
<tr>
<td>Biologics and Antineoplastics</td>
<td>Efalizumab, imatinib, sorafenib, vismodegib, vemurafenib</td>
</tr>
<tr>
<td>Antipyretics/Analgesics</td>
<td>Acetaminophen, celecoxib, diclofenac, ibuprofen</td>
</tr>
<tr>
<td>Others</td>
<td>Allopurinol, epoetin alfa, mexiletine, omeprazole, ranitidine</td>
</tr>
</tbody>
</table>

## Internal Organ Impact

<table>
<thead>
<tr>
<th>Medication</th>
<th>Associated Internal Organ</th>
</tr>
</thead>
<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, and cardiac</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Hepatic</td>
</tr>
</tbody>
</table>

Learning Assessment – Question 2

Which of the following medications are most likely to cause DRESS syndrome?

A. Carbamazepine, lamotrigine, and diltiazem

B. Fluoxetine, olanzapine, and vancomycin

C. Aspirin, ibuprofen, and valproic acid

D. Allopurinol, carbamazepine, and phenytoin
Learning Assessment – Question 2

Which of the following medications are most likely to cause DRESS syndrome?

A. Carbamazepine, lamotrigine, and diltiazem
B. Fluoxetine, olanzapine, and vancomycin
C. Aspirin, ibuprofen, and valproic acid
D. Allopurinol, carbamazepine, and phenytoin
Pathophysiology

- Not well understood
- Type IVb hypersensitivity
- Implicated mechanisms
  - Enzymatic abnormalities
  - Genetic predisposition of certain HLA alleles
  - Viral reactivation

HLA = human leukocyte antigen

Pathophysiology

A = enzymatic abnormalities and metabolite interaction with cellular components
B = medication or metabolite interaction with HLA
C = auto-immune response
D = reactivation of HHVs
E = anti-viral immunological response

HLA = human leukocyte antigen
HHV = human herpes virus

## Immunologic Pharmacogenomics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Associated Alleles</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>HLA-B*5801</td>
<td>Han Chinese, European, Thai, Korean</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-A<em>3101, HLA-A</em>11, HLA-B*51</td>
<td>Han Chinese, European, Japanese</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>HLA-B<em>1301, HLA-B</em>51101</td>
<td>Han Chinese</td>
</tr>
<tr>
<td>Dapsone</td>
<td>HLA-B*1301</td>
<td>Han Chinese</td>
</tr>
<tr>
<td>Abacavir†</td>
<td>HLA-B*5701</td>
<td>European</td>
</tr>
<tr>
<td>Nevirapine†</td>
<td>HLA-DRB1<em>0101, HLA-DRB1</em>0102, HLA-Cw8-B14, HLA-Cw8<em>4, HLA-B</em>3505</td>
<td>African, Asian, European</td>
</tr>
</tbody>
</table>

† = Unclear if the hypersensitivity reactions would meet the DRESS criteria as set forth by Karduan et al. 2013

**HLA = human leukocyte antigen**

Diagnosis

• Clinical similarities
• Variable presentation, course, and severity
• Relatively late onset
• Gradual evolution and long duration
• Continuation after removal of offending agent
• Atypical presentation

## DRESS Scoring System

<table>
<thead>
<tr>
<th>Item</th>
<th>Present</th>
<th>Absent</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥38.5°C</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Enlarged lymph nodes (≥1 cm at ≥2 sites)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eosinophilia: ≥0.7 x 10^9/L or ≥10% (if WBC &lt;4 x 10^9/L)</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>≥1.5 x 10^9/L or ≥20% (if WBC &lt;4 x 10^9/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytes</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash &gt;50% of BSA</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash suggestive (≥2 of facial edema, purpura, infiltration, desquamation)</td>
<td>1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Skin biopsy suggesting alternative diagnosis</td>
<td>-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Organ involvement: one</td>
<td>two or more</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rash duration ≥15 days</td>
<td>0</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Investigation for alternative cause (blood culture, ANA, serology for hepatitis viruses, Mycoplasma, Chlamydia) ≥3 done and negative</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Total Score:**
- <2 = excluded
- 2-3 = possible
- 4-5 = probable
- ≥6 = definite

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## Comparison to Other Drug-Induced Dermatological Reactions

<table>
<thead>
<tr>
<th>Reaction Type</th>
<th>Onset After Drug Exposure</th>
<th>Duration</th>
<th>Mucosal Involvement</th>
<th>Eosinophilia</th>
<th>Internal Organ Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRESS</td>
<td>2-6 weeks</td>
<td>Several weeks</td>
<td>~50% Typically 1 site most commonly oral cavity or lips</td>
<td>Yes often grade 2</td>
<td>Typically</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>1-3 weeks</td>
<td>1-3 weeks</td>
<td>≥90% Typically ≥2 sites</td>
<td>No</td>
<td>Typically</td>
</tr>
<tr>
<td>AGEP</td>
<td>≤2 days</td>
<td>&lt;1 week</td>
<td>Rare</td>
<td>Yes often mild</td>
<td>Rarely</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>1-3 weeks</td>
<td>Several weeks</td>
<td>Rare to ~35%</td>
<td>Yes often mild</td>
<td>Rarely</td>
</tr>
</tbody>
</table>

SJS/TEN = Stevens-Johnson syndrome / toxic epidermal necrolysis  
AGEP = acute generalized exanthematous pustulosis  
Learning Assessment – Question 3

What is one definitive difference between Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis and DRESS Syndrome?

A. Timeframe of emergence
B. Body surface area of rash
C. Eosinophilia
D. Internal organ involvement
Learning Assessment – Question 3

What is one definitive difference between Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis and DRESS Syndrome?

A. Timeframe of emergence
B. Body surface area of rash
C. **Eosinophilia**
D. Internal organ involvement
Acute Management

- Admit to ICU or burn unit
- Identify and discontinue offending agent
- Avoid new medications during the acute phase
- Rechallenging not recommended
  - Reaction within hours to days
- Dependent on severity and organ involvement

Corticosteroid Treatment

• High dose systemic corticosteroids
  • $\geq 1$ mg/kg/day prednisone equivalents tapered over 3 to 6 months
  • IV methylprednisolone pulse dosing at 30 mg/kg/day for 3 days for inadequate response

• Very high potency topical corticosteroids
  • Symptomatic relief
Other Treatments

- Immunosuppressants
  - Cyclosporine has strongest evidence
- IVIG 1 g/kg/day for 2 days
  - Conflicting data, not recommended
- N-acetylcysteine
  - Lack of data
- Plasmapheresis
  - Lack of data

IVIG = intravenous immunoglobulin

Supportive Therapies

• Fluids
• Electrolyte replacement
• Nutritional support
• Antihistamines
• Antipyretics
• Antivirals
Learning Assessment – Question 4

After withdrawal of the suspected causative agent, which of the following is the most appropriate treatment for severe symptomatic DRESS syndrome?

A. IVIG 1-2 g/kg/day for 2 days

B. IV corticosteroids 0.5 mg/kg/day prednisone equivalents initially and tapered over 5-7 days

C. IV corticosteroids 1 mg/kg/day prednisone equivalents initially and tapered over 3-6 months

D. Topical clobetasol 0.05% applied to the affected areas three times daily for 7 days
Learning Assessment – Question 4

After withdrawal of the suspected causative agent, which of the following is the most appropriate treatment for severe symptomatic DRESS syndrome?

A. IVIG 1-2 g/kg/day for 2 days

B. IV corticosteroids 0.5 mg/kg/day prednisone equivalents initially and tapered over 5-7 days

C. **IV corticosteroids 1 mg/kg/day prednisone equivalents initially and tapered over 3-6 months**

D. Topical clobetasol 0.05% applied to the affected areas three times daily for 7 days
### Potential Assessment Parameters

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>CBC, LFTs, BMP, CPK, LDH, ferritin, triglycerides, calcium, 24 hour urine protein and eosinophil count, PTH, TSH, BG, PT, PTT, lipase, protein electrophoresis, CRP, quantitative PCR for HHVs, blood culture, ANA panel</td>
</tr>
<tr>
<td><strong>Daily</strong></td>
<td>BMP, CBC, LFTs, ID</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>LFTs, PT, PTT, INR, hepatitis Panel</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>EKG, echocardiogram, cardiac enzymes</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>CXR, PFTs</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>sCr, BUN, urinalysis, renal US</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>TSH/T4, BG</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Fecal occult blood test, lipase</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td>CT/MRI head, EEG, CSF analysis</td>
</tr>
</tbody>
</table>

References


References


Questions?