Dermatologic Emergencies

Mark A. Bechtel, MD
Clinical Associate Professor
Division Director, Dermatology
Ohio State University Medical Center

Life-Threatening Drug Reactions

- Stevens Johnson Syndrome (SJS)
- Toxic Epidermal Necrolysis (TEN)
Clinical Features of SJS/TEN

- Initial symptoms
  - Fever, stinging eyes, pain on swallowing
  - Mucositis may precede skin lesions by a few days

- Skin lesions
  - Appear first on trunk, spread to neck, face, proximal extremities with maximal involvement within 4 days
  - Rash is often dusky, erythematous, may demonstrate bullae, separation of large sheets of epidermis from dermis
  - Skin is very TENDER

Clinical Features of SJS and TEN

<table>
<thead>
<tr>
<th></th>
<th>SJS</th>
<th>SJS-TEN</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA% detachment</td>
<td>&lt; 10</td>
<td>10-30</td>
<td>&gt; 30</td>
</tr>
</tbody>
</table>
What is the incidence of SJS and TEN?

- **Stevens-Johnson Syndrome**
  - Rate is 1 to 7 cases per million per year
  - Mortality – 1-3% for adults; 7.5% for children

- **Toxic Epidermal Necrolysis**
  - Rate is 2 cases per million per year
  - Mortality – 30%

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Drugs are the major cause of TEN
More than 220 medications are reported to cause TEN

- trimethoprim/sulfamethoxazole
- anticonvulsants – may crossreact with each other
  - phenytoin
  - phenobarbital
  - carbamazepine
- β-lactam antibiotics
- nevirapine
- abacavir
- non-steroidal anti-inflammatory drugs (oxicams)
  - allopurinol
  - lamotrigine
  - quinolones (ciprofloxacin)
  - tetracycline family
  - aminopenicillins
### Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- **Rare Causes**
  - Vaccinations (MMR)
  - Industrial chemicals
  - Fumigants
  - Intranasal application of mupirocin
  - Pseudoephedrine
  - “natural” medications and Chinese herbal medications

### Important Drug Causes of SJS/TEN in Children

- sulfonamides
- phenobarbital
- carbamazepine
- lamotrigine
Steven-Johnson Syndrome (SJS) in Children

- Infections most important cause
  - Mycoplasma pneumoniae
  - Herpes simplex virus
  - Mycobacterium tuberculosis
  - Group A streptococci
  - Hepatitis B virus
  - Epstein-Barr virus

Genetic Factors in SJS/TEN

- HLA-B 1502 – strongly associated in patients of Chinese/Asian ethnicity with carbamazepine-induced SJS/TEN.
- Han Chinese with HLA-B 1502 are especially at risk of developing STS/TEN from carbamazepine
- No correlation between HLA-B 1502 with carbamazepine and caucasians
- Strong association between HLA-B 5801 and allopurinol reaction
- HLA-B 5801 also associated with allopurinol-induced SJS/TEN in Europeans
Lamotrigine (Lamictal®) Drug Reactions

- 10% of patients develop erythema and a maculopapular eruption
- Eruption usually develops during the first 2-8 weeks of therapy
- Life-threatening eruptions are more common in children than in adults
  - 1 in 100 pediatric patients
  - 3 in 1000 adult patients

Lamotrigine (Lamictal®)

- 1% of patients develop
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Angioedema
  - Pruritus
  - Multi-organ dysfunction (hepatic, DIC)
## Predictors of Lamotrigine-associated rash

- Previous eruption from an anti-epileptic medication is the most likely predictor
- Children < 13 years of age
- Co-medication with valproic acid
- Female patient
Mucocutaneous Lesions

- Occur in 90% of patients
  - Lips
  - Oral cavity
  - Conjunctiva
  - Nasal cavity
  - Urethra
  - Vagina
  - Gastrointestinal tract
  - Respiratory tract
### Ocular Sequelae Most Serious

- Early ophthalmologic consultation advised
- Synechiae
- Corneal ulcers
- Xerophthalmia
- Symplepharon
- Blindness

### Respiratory Tract Involvement with TEN

- Epithelium of respiratory tract involved in 25% of patients
- Involvement of the respiratory mucosa is insidious
- Serious pulmonary complications can occur with a normal chest x-ray
- Clinical signs
  - Dyspnea
  - Tachypnea
  - Hypoxemia
<table>
<thead>
<tr>
<th>Erythema Multiforme (EM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Now considered a different disease than SJS/TEN</td>
</tr>
<tr>
<td>• Typical or raised atypical target lesions distributed acrally</td>
</tr>
<tr>
<td>• Mucositis – involves only oral mucosa</td>
</tr>
<tr>
<td>• PCR assays reveal the DNA of herpes simplex virus of lesional skin in the majority of patients</td>
</tr>
<tr>
<td>• Patients are usually young, healthy, mild clinical course, frequent recurrences</td>
</tr>
</tbody>
</table>

![Image of Erythema Multiforme](image_url)
SJS/TEN – Contrast to EM

- SJS/TEN more severe than EM and patients febrile and prostrate
- SJS/TEN usually caused by medications
- Distribution of lesions in SJS/TEN are predominately central with involvement of two mucosal sites
- Lesions are flat, atypical targets or purpuric macules
Scorten-prognostic scoring system for patients with TEN

- **Prognostic factors**
  - Age > 40
  - HR > 120 bpm
  - Cancer or hematologic malignancy
  - BSA on day 1 >10%
  - Serum urine level (>10mmol/l)
  - Serum bicarbonate level (<20mmol/l)
  - Serum glucose level (14mmol/l)

- **Points**
  - 1
  - 1
  - 1
  - 1
  - 1

- **Scorten**
  - 0-1
  - 2
  - 3
  - 4
  - >5

- **Mortality Rate**
  - 3.2
  - 12.1
  - 35.8
  - 58.3
  - 90

Treatment of Patients with SJS/TEN

- Promptly discontinue any and all possible offending drugs
- Admit to skilled nursing unit – ICU or burn unit
- Correct fluid and electrolyte imbalances
- Caloric replacement
- Ophthalmologic consult
- Urology consult, if urethral inflammation
### Treatment of Patients with SJS/TEN

- Pulmonary toilet
- Periodic cultures of mouth, eyes, skin, sputum
- Physical therapy
- Debridement of necrotic epidermis and coverage of denuded areas
- Artificial membranes – Biobrane/biologic dressings, porcine xerografts, human skin

### Treatment of TEN

- Plasmapheresis
- Cyclosporine A 3 mg/kg
- Thalidomide – was shown to increase mortality
- Infliximab is currently being studied
Corticosteroids in TEN

- Many feel corticosteroids are best avoided
- Corticosteroids given 48 hours or more prior to admission were associated with increased mortality\(^1\)
- IV dexamethasone 1.5 mg/kg body weight for 3 consecutive days resulted in reduced mortality\(^2\)


IVIG in TEN

- A multicenter, retrospective study of 14 European and American university based medical centers (48 patients) – the survival rate was 88%.
- The recommended dose was IVIg 1g/kg/day for 3 days.
- Many studies published demonstrating no benefit in increased mortality.


- 281 patients with SJS or TEN were retrospectively studied.
- Evaluated patients treated with IVIg, IVIg + corticosteroids, corticosteroids, supportive care
- Not sufficient evidence that IVIg or corticosteroids are more beneficial than supportive care alone
- No support that IVIg has great clinical benefit
- Corticosteroids – there was a trend for clinical benefit

Clinical Features That Alert to a Possible Severe Drug-Induced Eruption

- Edema of the face
- Marked peripheral blood hypereosinophilia
- Mucous membrane lesions
- Painful or dusky skin
DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms

• Defect in the detoxification of anticonvulsants and sulfonamides
• Anticonvulsants – inability to detoxify toxic arene oxide metabolites
• Cross reactivity between phenytoin, carbamazepine, phenobarbital
• DRESS secondary to sulfonamides – acetylator phenotype and lymphocytic susceptibility to metabolite hydroxylamine
• Possible role of viruses HHV-6 and HHV-7

Clinical Features of DRESS

• Edema of the face is a hallmark of DRESS
• Morbilliform eruption that becomes edematous with a follicular accentuation
• Additional findings – vesicles, bullae, erythroderma, purpura, and pustules
**Other Features of DRESS**

- Lymph nodes enlarged
- Arthralgias
- Hepatitis – may be fulminant and leading cause of death (10% of cases)
- Myocarditis
- Interstitial pneumonitis
- Interstitial nephritis
- Thyroiditis
- Gastrointestinal bleeding – especially allopurinol
- Eosinophilia and atypical lymphocytes
### DRESS- Common Etiologies

- Aromatic anticonvulsants – phenobarbital, carbamazepine, phenytoin
- Lamotrigine (especially when co-administered with valproate)
- Sulfonamides
- Minocycline
- Allopurinol – full doses in setting of renal failure
- Gold salts
- Dapsone
- HIV drugs – especially abacavir

### Therapy of DRESS

- Early withdrawal of offending drug
- Corticosteroids are first line
- Topical steroids for milder cases
- Systemic steroids are especially helpful for heart and lung involvement, but kidneys and liver are less responsive
Necrotizing Fasciitis

- Rapidly progressing necrosis of subcutaneous fat and fascia, which can be life-threatening
- Approximately 500-1500 cases each year
- Mortality 20-40%
- Group A strep (10% of cases)
- Most cases are mixed infection of aerobic and anaerobic bacteria

Common Clinical Settings

- Elderly patients
- Diabetes
- Cardiac and peripheral vascular disease
- Alcoholism
- Penetrating or blunt trauma
- Varicella
- Decubitus or ischemic ulcers
- Recent surgery
- Young, previously healthy individuals
### Risk Factors Associated With Higher Mortality

- Female sex
- Older age
- Greater extent of infection
- Delay to first debridement
- Elevated serum creatinine or lactic acid
- Group A strep
- Greater degree of organ dysfunction at time of admission
Bacterial Etiology

- 10% of cases are caused by group A streptococci
- Majority of cases due to a mixed infection of anaerobic and aerobic bacteria
  - Group A strep
  - S. aureus (including MRSA)
  - E. coli
  - Bacteroides
  - Pseudomonas aeruginosa
  - H. influenzae
  - Aeromonas hydrophila
  - V. vulnificus

Clinical Features

- Exquisitely tender, erythematous, swollen, tender cellulitis, which does not respond to antibiotics
- Disease progresses at an alarming rate from red to purple
- Pathognomonic sign is a gray-blue, ill-defined patch, sometimes with bullae
- Necrosis of superficial fascia and fat produces a thin, watery, malodorous fluid
Clinical Features

- Becomes anesthetic as cutaneous nerves are destroyed
- Patients become extremely toxic
- Extremities most commonly involved, followed by perineum and genitalia (Fournier’s gangrene)

Prognosis

- Presence of anesthesia suggests a deeper component
- MRI helps delineate depth of tissue involvement
  - Clues Severe pain
  - Rapidly spreading tense edema
  - Gray-blue discoloration
  - Foul-smelling discharge
  - Elevated CPK
### Initial Evaluation

- CBC, BUN, creatinine, electrolytes, CPK
- Blood cultures
- Wound swab for gram stain and culture
- Plain x-ray (soft tissue air is seen in minority of cases)
- Consider skin biopsy and tissue cultures

### Treatment

- Extensive surgical debridement (fasciotomy) is mainstay of treatment
- Amputation may be necessary
- Antimicrobial treatment directed from results of initial gram stain
- Initial antibiotics – β-lactam/β-lactamase inhibitor with broad spectrum coverage against gram-negative bacilli, staphylococci, streptococci, and anaerobes
<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>• Pseudomonas coverage for neutropenic patients</td>
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<tr>
<td>• Hyperbaric oxygen – anaerobic gram negative infection</td>
</tr>
<tr>
<td>• IVIg for patient with group A strep</td>
</tr>
<tr>
<td>• Nutritional support</td>
</tr>
<tr>
<td>• Reconstructive surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staphlococcal Scalded Skin Syndrome</th>
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<tbody>
<tr>
<td>• Primarily a disease of children less than 6 years of age</td>
</tr>
<tr>
<td>• Adults – chronic renal failure or immunosuppression</td>
</tr>
<tr>
<td>• Outbreaks in neonatal nurseries</td>
</tr>
<tr>
<td>• Phage group II strains of s. aureus (3A, 3C, 55, 71)</td>
</tr>
</tbody>
</table>
### Epidermolysins

- **Exfoliative toxin (ETA)** – chromosomally encoded
- **Exfoliative toxin (ETB)** – plasmid encoded
- Act on granular layer --> causes split and sterile bullae
- Specific for desmoglein 1
### Clinical Features of SSSS

- Prodrome of malaise, fever, irritability
- Severe skin TENDERNESS
- Purulent rhinorrhea or conjunctivitis
- Wrinkled appearance due to flaccid bullae
- Nikolsky sign positive
- Bullae slough causing a varnish-like crust
- Flexural areas first to exfoliate
- Perioral crusting and radial fissuring

### Treatment of SSSS

- If extensive – hospitalization and parenteral antibiotics
- β-lactamase-resistant antibiotics for minimum of one week
- Denuded areas – bland emollients
- Identification and treatment of s. aureus carriers
**TEN versus SSSS**

<table>
<thead>
<tr>
<th></th>
<th>TEN</th>
<th>SSSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cause</td>
<td>usually drug</td>
<td>s. aureus toxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>producing</td>
</tr>
<tr>
<td>age</td>
<td>adults</td>
<td>infants, young children</td>
</tr>
<tr>
<td>histology</td>
<td>D/E separation</td>
<td>granular layer split.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dermis lacks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inflammation</td>
</tr>
<tr>
<td>distribution</td>
<td>areas of sparing</td>
<td>generalized, flexural</td>
</tr>
<tr>
<td></td>
<td></td>
<td>accentuation</td>
</tr>
<tr>
<td>mucous membranes</td>
<td>involved</td>
<td>uninvolved</td>
</tr>
<tr>
<td>Nikolsky sign</td>
<td>present</td>
<td>may be present in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>uninvolved skin</td>
</tr>
<tr>
<td>face</td>
<td>lips involved</td>
<td>perioral crusting, radial skin fissures</td>
</tr>
</tbody>
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**Toxic Shock Syndrome**

- Early 1980’s – most cases were in young menstruating white women
- Currently, most cases “non-menstrual”, surgical procedures, cutaneous pyodermas, postpartum infections, deep abscesses, infected nasal packing or insulin pump infusions
- Staph aureus produces toxic shock syndrome toxin-1 (TSST-1), which is found in 90% of cases
- Patients with no antibodies to TSST-1 are at risk
Toxic Shock Syndrome

- Fever > 39.6 C (102 F)
- Rash – diffuse macular erythoderma
- Desquamation: 1-2 weeks after the onset of illness (hands, feet)
- Hypotension: systolic blood pressure < 90mm Hg

Toxic Shock Syndrome

- Involvement of three or more of the following organ systems:
  - Gastrointestinal
  - Muscular
  - Central nervous
  - Renal
  - Hepatic
  - Mucous membrane (erythema)
  - Hematologic (platelets < 100,000/mm³)
## Treatment of TSS

- Intensive supportive therapy
- Hypotension – intravenous fluids and vasopressor agents
- Any nidus of infection should be removed
- β-lactamase-resistant antibiotics
- Consider clindamycin to suppress toxin production

## Streptococcal Toxic Shock

- Isolation of group A strep from normally sterile site (blood, cerebrospinal fluid, tissue biopsy)
- Hypotension – systolic blood pressure < 90
- Two or more of the following:
  - Renal impairment
  - Coagulopathy (platelets < 100,000)
  - Liver impairment
  - Adult respiratory distress syndrome
  - Generalized erythematous macular rash
  - Soft tissue necrosis
### Streptococcal Toxic Shock Syndrome

- A disruption of the cutaneous barrier is a portal of entry
- 50% of patients have no known source for their streptococcal bacteremia
- Streptococcal pyogenes strains (M types 1 and 3) are common culprit
- Release streptococcal pyogenic toxins A, B, or both

### Streptococcal Toxic Shock Syndrome

- Toxins act as superantigens and induce TNF-alpha and IL-1
- Most common initial symptom is severe local pain in an extremity
- 50% of patients show signs of underlying soft tissue infection
Treatment of Streptococcal Toxic Shock Syndrome

- Intensive supportive therapy
- Hypotension – aggressive intravenous fluid and vasopressors
- Clindamycin inhibits production of bacterial toxins
- Early surgical intervention

Toxic Shock Syndromes (Staph versus Strep)

<table>
<thead>
<tr>
<th></th>
<th>staphylococcal</th>
<th>streptococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>typical patient</td>
<td>young (15-35), healthy</td>
<td>young (20-25), healthy</td>
</tr>
<tr>
<td>diffuse macular erythema</td>
<td>very common</td>
<td>less common</td>
</tr>
<tr>
<td>localized extremity pain</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>hypotension</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>renal failure</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td>predisposing</td>
<td>surgical packs, abscesses, tampons</td>
<td>laceration, bites, varicella</td>
</tr>
</tbody>
</table>
Purpura Fulminans

- DIC with skin necrosis secondary to thrombosis
- **Associations**
  - Newborns with homozygous protein C deficiency
  - Acute infections (varicella, staph, meningococcus)
  - Metastatic malignancy
  - Trauma, surgical obstetrical procedures
  - Part of heparin or warfarin necrosis
  - Antiphospholipid antibody syndrome