Dermatologic Emergencies

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

<table>
<thead>
<tr>
<th>Stevens-Johnson Syndrome</th>
<th>Toxic Epidermal Necrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate 1 to 7 cases per million per year</td>
<td>Rate 2 cases per million per year</td>
</tr>
<tr>
<td>Mortality – 1-3% for adults; 7.5% for children</td>
<td>Mortality – 30%</td>
</tr>
</tbody>
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### Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

<table>
<thead>
<tr>
<th>Rare Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinations (MMR)</td>
</tr>
<tr>
<td>Industrial chemicals</td>
</tr>
<tr>
<td>Fumigants</td>
</tr>
<tr>
<td>Intranasal application of mupirocin</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
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<tr>
<td>“natural” medications and Chinese herbal medications</td>
</tr>
</tbody>
</table>

### 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

### 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

### 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

### 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®)

- 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

### Erythema Multiforme (EM)
- Now considered a different disease than SJS/TEN
- Typical or raised atypical target lesions distributed acrally
- Mucositis – involves only oral mucosa
- PCR assays reveal the DNA of herpes simplex virus of lesional skin in the majority of patients
- Patients are usually young, healthy, mild clinical course, frequent recurrences
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

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40</td>
<td>1</td>
</tr>
<tr>
<td>HR &gt; 120 bpm</td>
<td>1</td>
</tr>
<tr>
<td>Cancer or hematologic malignancy</td>
<td>1</td>
</tr>
<tr>
<td>BSA on day 1 &gt;10%</td>
<td>1</td>
</tr>
<tr>
<td>Serum urine level (&gt;10mmol/l)</td>
<td>1</td>
</tr>
<tr>
<td>Serum bicarbonate level (&lt;20mmol/l)</td>
<td>1</td>
</tr>
<tr>
<td>Serum glucose level (14mmol/l)</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Scorten</th>
<th>Mortality Rate</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>3.2</td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>3</td>
<td>35.8</td>
</tr>
<tr>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>&gt;5</td>
<td>90</td>
</tr>
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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

Corticosteroids in TEN

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


Treatment of TEN

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

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

**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.

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

**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

**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

### Staphlococcal Scalded Skin Syndrome

- Primarily a disease of children less than 6 years of age
- Adults – chronic renal failure or immunosuppression
- Outbreaks in neonatal nurseries
- Phage group II strains of *S. aureus* (3A, 3C, 55, 71)
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><strong>cause</strong></td>
<td>usually drug-producing S. aureus toxins</td>
<td>infants, young children</td>
</tr>
<tr>
<td><strong>age</strong></td>
<td>adults</td>
<td>young children</td>
</tr>
<tr>
<td><strong>histology</strong></td>
<td>D/E separation</td>
<td>granular layer splitting, dermis lacks inflammation</td>
</tr>
<tr>
<td><strong>distribution</strong></td>
<td>areas of sparing</td>
<td>generalized, flexural accentuation</td>
</tr>
<tr>
<td><strong>mucous membranes</strong></td>
<td>involved</td>
<td>uninvolved</td>
</tr>
<tr>
<td><strong>Nikolsky sign</strong></td>
<td>present</td>
<td>may be present in uninvolved skin</td>
</tr>
<tr>
<td><strong>face</strong></td>
<td>lips involved</td>
<td>perioral crusting, radial skin fissures</td>
</tr>
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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 erythroderma
- 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 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

- 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

- 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

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

Toxic Shock Syndromes (Staph versus Strep)

<table>
<thead>
<tr>
<th></th>
<th>Staphylococcal</th>
<th>Streptococcal</th>
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<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>
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