Dermatologic Emergencies

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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

Life-Threatening Drug Reactions

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

Clinical Features of SJS and TEN

	SJS	SJS-TEN	TEN
BSA% detachment	< 10	10-30	> 30

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%

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

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

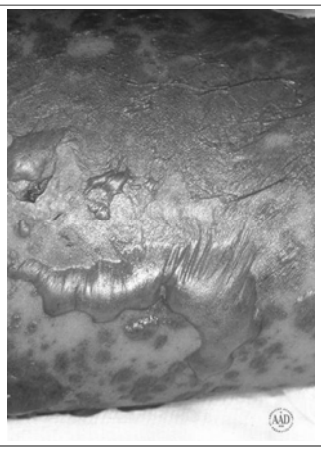
- HLA-B 1502 – strongly associated in patients of Chinese/Asian ethnicity with carbamazepine-induced SJS/TEN.
- Han Chinese with HLA-B 1502 are especially at risk of developing STS/TEN from carbamazepine
- No correlation between HLA-B 1502 with carbamazepine and caucasians
- Strong association between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

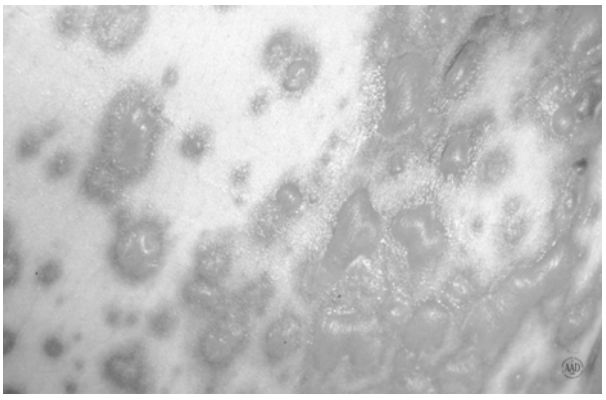
Lamotrigine (Lamictal®)

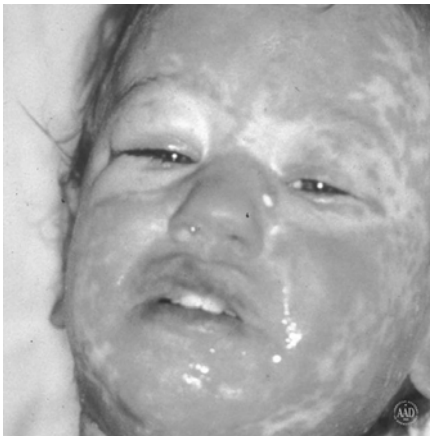
- 1% of patients develop
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Angioedema
  - Pruritus
  - Multi-organ dysfunction (hepatic, DIC)

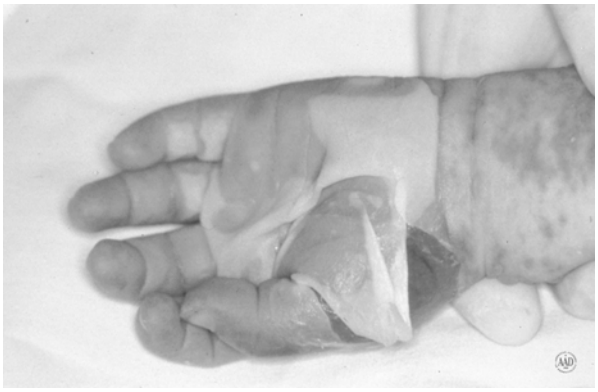
Predictors of Lamotrigine-associated rash

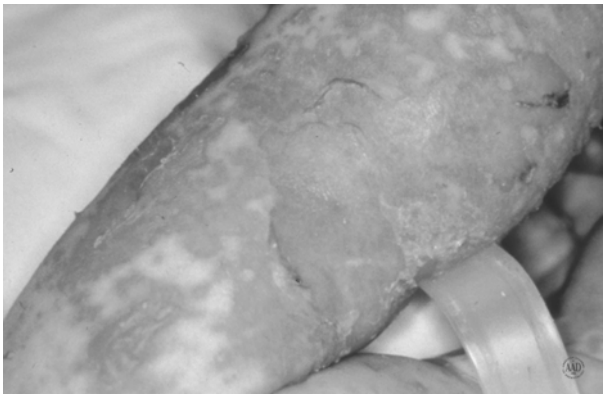
- Previous eruption from an anti-epileptic medication is the most likely predictor
- Children < 13 years of age
- Co- medication with valproic acid
- Female patient











Mucocutaneous Lesions

- Occur in 90% of patients
  - Lips
  - Oral cavity
  - Conjunctiva
  - Nasal cavity
  - Urethra
  - Vagina
  - Gastrointestinal tract
  - Respiratory tract

Ocular Sequelae Most Serious

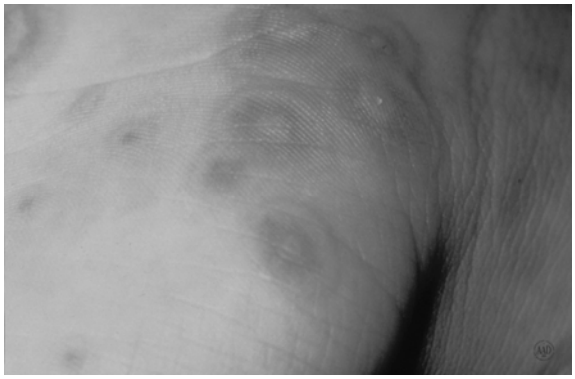
- Early opthalmologic consultation advised
- Synechiae
- Corneal ulcers
- Xerophthalmia
- Symplepharon
- Blindness

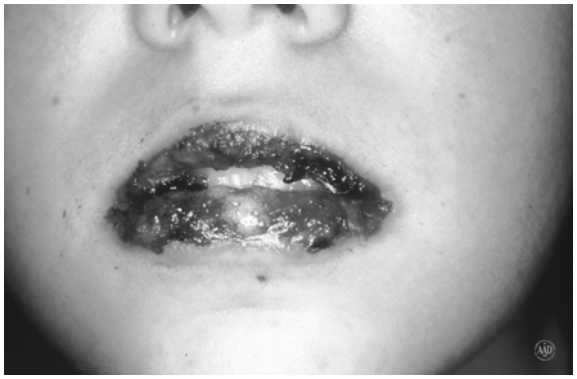
Erythema Multiforme (EM)

- 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

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





Scorten-prognostic scoring system for patients with TEN

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

Scorten	Mortality Rate
0-1	3.2
2	12.1
3	35.8
4	58.3
>5	90

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

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[1]
- IV dexamethasone 1.5 mg/kg body weight for 3 consecutive days resulted in reduced mortality[2]

1. Engelhardt SL. *J Burn Care Rehabil* 1997; 18:520-4.
2. Kardaun SH. *Acta Derm Venereol* 2007; 87: 144-148.

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.

1. Prins C. *Arch Dermatol* 2003; 139: 26-32.

- **Effects of treatment on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR study. Schneck J. *J Am Acad Derm* 2008; 58: 33-40.**
  - **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**

DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms

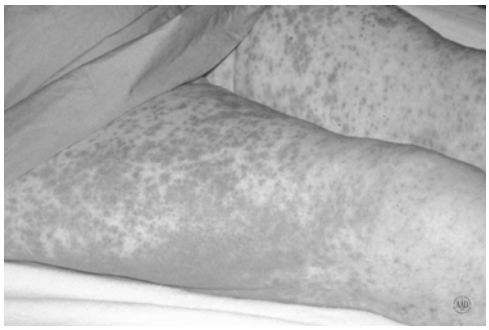
- **Defect in the detoxification of anticonvulsants and sulfonamides**
- **Anticonvulsants – inability to detoxify toxic arene oxide metabolites**
- **Cross reactivity between phenytoin, carbamazephine, phenobarbital**
- **DRESS secondary to sulfonamides – acetylator phenotype and lymphocytic susceptibility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

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- Common Etiologies

- Aromatic anticonvulsants – phenobarbitol, 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

Other Features of DRESS

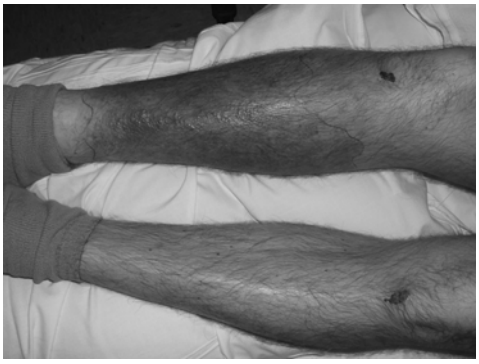
- Lymph nodes enlarged
- Arthralgias
- Hepatitis – may be fulminant and leading cause of death (10% of cases)
- Myocarditis
- Interstitial pneumonitis
- Interstitial nephritis
- Thyroiditis
- Gastrointestinal bleeding – especially allopurinol
- Eosinophilia and atypical lymphocytes

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

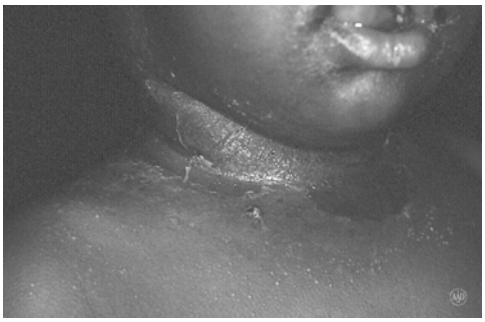
- Pseudomonas coverage for neutropenic patients
- Hyperbaric oxygen – anaerobic gram negative infection
- IVIg for patient with group A strep
- Nutritional support
- Reconstructive surgery

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



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

Epidermolysins

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

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

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

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

- **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

- **Involvement of three or more of the following organ systems:**
  - **Gastrointestinal**
  - **Muscular**
  - **Central nervous**
  - **Renal**
  - **Hepatic**
  - **Mucous membrane (erythema)**
  - **Hematologic (platelets < 100,000/mm^3)**

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)

	staphylococcal	streptococcal
typical patient	young (15-35), healthy	young (20-25), healthy
diffuse macular erythema	very common	less common
localized extremity pain	rare	common
Soft tissue infection	rare	common
hypotension	100%	100%
renal failure	common	common
predisposing	surgical packs, abscesses, tampons	laceration, bites, varicella