More Than Just a Rash: Pediatric Life Threatening Systemic Illnesses

Shari Simone, DNP, CPNP-AC, FCCM

Objectives

- Present an overview of Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis
  - Etiologies
  - Clinical manifestations
  - Diagnosis & differential diagnoses
  - Patient management
  - Specific therapies based on current evidence
- Present case studies
  - Discussion of critical nursing strategies

“an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis”

………..Described by Stevens and Johnson in 1922
In 1956 Lyell described......

“Four patients with extensive loss of the epidermis due to necrosis leaving the skin looking scalded”

...coined the term toxic epidermal necrolysis

---

Introduction

- Spectrum of mucocutaneous disorders with similar clinical features
- EM
  - different etiology
- SJS & TEN
  - single disease
  - etiology same
  - histopathophysiology
  - management
  - complications

---

Erythema Multiforme

- Acute self-limited skin eruption
- Usually occurs after infections
- Nonspecific prodrome
  - EM minor – mild resp. infection, rash with 3 days
  - EM major – fever, sore throat, symptoms may present 1-2 weeks before rash
- Rash usually on extremities, spares trunk & mucous membranes
- Hallmark is a target lesion
  - Inner ring: bright pink or red
  - Outer ring: lighter pink
  - Outermost ring: darker pink
- Benign course
  - EM minor - onset to healing about 2-4 weeks
  - EM major usually takes 3-6 weeks
Stevens-Johnson Syndrome

- Incidence 1 to 6 cases/million/year (Gerull et al., 2011)
- Etiologies
  - Medications
    - Anticonvulsants, antibiotics, NSAIDs, over-the-counter
  - Symptoms occur 1-3 weeks after initial exposure
  - Infection:
    - Mycoplasma, viral, Staphylococcal sp.
  - GVHD, allergy, immunizations, malignancy

SJS: Clinical Manifestations

- May present as a febrile illness 1-3 days before rash erupts
  - Fever, sore throat, chills, cough, minteria, malaise
- Atypical lesions
  - Flat, purpuric macules also blisters/bulla, ulcers
  - Predominately over trunk, face, anterior surface of extremities, palms & soles
  - Becomes confluent
  - Painful, pruritic
- Skin involvement is < 10% BSA
  - Progression of rash over several days
  - + mucosal involvement

Mucosal / Visceral Involvement

- 92.3%-100% incidence
- At least 2 mucous membranes
  - Oral- buccal & tongue
  - Conjunctiva / ocular
  - Tracheal / Bronchial
  - Gastrointestinal
  - Genitalia
  - Hepatic
  - Renal
  - Skin < 10% total BSA
Toxic Epidermal Necrolysis

- Incidence
  - 0.4-1.5 cases/million/yr (Guerull et al, 2011)
- Similar etiologies as SJS
- Clinical manifestations are more severe
- Skin involvement is > 30%
- Nikolsky’s sign
- Increased complications
  - Multi-system
  - Mortality (25-30%)

Pathophysiology

- Exact mechanism unknown
- Theories (Stella et al, 2007):
  - Altered drug metabolism → formation of reactive metabolites → bind to & alter cell proteins → triggers a T-cell mediated cytotoxic reaction to drug antigens in keratinocytes
  - Interaction between Fas (a cell-surface death receptor) and its ligand induce keratinocyte apoptosis (Virard et al, 1998)
- Results in separation of the epidermis from the dermis

Diagnosis of SJS/TEN

- Primarily based on clinical findings
- Laboratory data not helpful
- Skin biopsy
  - Rules out other etiologies
  - Findings
    - Early: infiltration of lymphocytes & macrophages in the epidermis
    - Late: cell-poor infiltrate, full thickness epidermal necrosis, separation of dermal-epidermal junction
What is Your Diagnosis?

- 5 yr old caucasian male w/o significant PMH who presents to the ER with fever, lip swelling, oral lesions, rash, & inability to tolerate PO intake. No drooling, no WOB
- PE: Periorbital edema, swollen lips, cracked with dried blood, blistering lip & oral lesions, red, macular, erythematosus rash over face, abdomen, back, palms & soles

SJS, TEN, or something else?

Differential Diagnosis: Staphylococcal Scalded Skin Syndrome

- Etiology: Staph infection releases exotoxin
- Clinical Symptoms:
  - Abrupt onset of fever, irritability
  - Rash: diffuse, blanching erythematous, & bullae rupture & separate superficial epidermis into sheets (Nikolsky's sign)
  - Mucosal involvement: limited, except desquamation of lips
- Diagnosis: skin biopsy reveals cleavage in sub epidermis, + culture

Treatment of SSSS

- Initial treatment always with
  - Methicillin-resistant Staphylococcal antibiotic coverage
  - Serial Vancomycin levels if decreased renal function
- Fluid & electrolyte management
- Wound care/isolation
- Pain management
- Prevent hypothermia & secondary infection
Differential Diagnosis: Kawasaki’s Syndrome

- Vasculitic syndrome
- Based on clinical features:
  - Fever for ≥ 5 days & 4 of 5 features
  - Non-vesicular rash
  - Cervical lymphadenopathy
  - Erythema of palms or soles
  - Oral mucosal changes & strawberry tongue
  - Conjunctival injection
- Atypical/Incomplete Kawasaki’s
  - Fever & < 4 signs of mucocutaneous inflammation
  - Or additional feature not typical of Kawasaki’s

Specific Treatment of Kawasaki’s Syndrome

- High dose ASA (80-100 mg/kg/day ÷ q 6 hrs)
  - (Baumer et al, Cochrane Database Syst Rev, 2003)
- IVIG 2 gm/kg over 12 hrs
  - (Oates-Whitehead et al, Cochrane Database Sys Rev, 2006)
  - Findings reveal decrease in coronary artery aneurysm development
  - Single 2 gm/kg vs. 400 mg/kg for 4 days recommended
- Low dose ASA (3-5 mg/kg/day)
  - Greater than 48-72 hrs after resolution of fever
  - Dc if normal ECHO at 6-8 wks

Differential Diagnosis: Toxic Shock Syndrome

- Etiology: toxin-mediated Staphylococcus aureus or Streptococcus pyogenes (GAS) infection
- Clinical signs: fever, hypotension & rash
  - Diffuse, erythematous macular
    - (trunk → ext → palms/soles)
  - Desquamation of palms & soles late sign
- AND multisystem involvement
- Diagnosis: CDC criteria
Treatment for TSS

- Hemodynamic support
- Empiric antibiotic therapy
  - Vancomycin, Ceftriaxone, & Clindamycin
- Early surgical exploration with clinical evidence of NF
- Reports of IVIG benefits
  - (Lappin & Ferguson, 2009)
- Management of multisystem complications

Differential Diagnosis: DRESS

- Drug rash, eosinophilia, systemic symptoms syndrome (Bucquet, 1996)
  - Incidence: 1-5,000 to 10,000
  - Mechanism: Detoxification defect & viral co-infection
  - Clinical Features:
    - Maculopapular rash 2-6 wks after initiating drug
    - Visceral involvement
    - No mucosal involvement

Treatment of DRESS

- Primary treatment is stopping offending drug
- IV Corticosteroids controversial
  - 2 mg/kg/day + q 6 hr, tapered
  - Complications
    - Delayed wound healing
    - Increased risk of infection
    - Mask early signs of infection
    - Increased risk of GI bleeding
- Antihistamines
Case Progression

- Culture + for mycoplasma
- Treated with azithromycin
- Increased progression of rash plus mucosal involvement
- Biopsy + for SJS
- Intubated & ventilated for 4 days
- Improvement seen following IVIG
- Received supportive care including aggressive eye & wound care
- Good outcome

Case Study # 2

- 6 yo male with history of asthma & atopic dermatitis who presented to OSH with fever & rash
- Well until 2 wks PTA, seen at urgent care clinic for left wrist abscess
- Treated with 10 day course of amoxicillin with resolution (3 days PTA)
- 2 Days PTA, developed fever to 100.3 & facial rash, returned to urgent care clinic, rapid strep negative & augmentin initiated
- Fever 103 - given ibuprofen

Case Study: ER Course

- DOA fever 106, throat pain, & worsening rash
- Taken to outlying ER – c/o sore throat, pain with cough, penile pain,
- Exam revealed diffuse macular rash over face & extremities, blisters on L pinna, injected sclera, crusting on lips, erythematous pharynx
- Treated with IV NS bolus, benadryl, solumedrol, pepcid, tylenol, & clindamycin
- R/O staphylococcal scalded skin syndrome (SSSS)
- Transferred to PICU
Case Study: PMH

- Med conditions: mild intermittent asthma, eczema
- 1 previous adm: croup
- Surgical history: circumcision
- IMM: UTD, no flu vaccine
- Meds: Albuterol prn, motrin, augmentin
- Fm Hx: mother with asthma
- Soc Hx: lives with parents, 2 brothers (healthy), + tobacco exposure, no pets, + carpets
- Dev: NL, 1st grade

Case Study: PICU Exam

VS: T 98.2, HR 125, Bp 115/75, RR 21, SpO2 100% in RA
Gen: Nontoxic appearing child
HEENT: Mild periorbital & facial edema, left ear blisters, desquamation, conjunctiva injected, nares patent, lips edematous, eroded with hemorrhagic crusts, bullae on cheeks, pharynx erythematous, no oral lesions
Chest: BS CTA, no WOB
CV: SR, NL S1, S2, no murmur, pulses +2 = bil, brisk CRT
Abd: BS +, soft, ND, NT, no HSM
GU: tanner 1, crusting at urethral meatus
Neuro: A & O, PERRL, CN II-XII intact, strength +5/5
Skin: maculopapular diffuse rash, vesicles over face, chest, abdomen, & UE, eczematous patches on posterior knees

Case Study: Initial Lab Data

<table>
<thead>
<tr>
<th>Lactate</th>
<th>LFTs: normal</th>
<th>CRP: 3.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>3.9</td>
<td>135</td>
</tr>
<tr>
<td>69</td>
<td>105</td>
<td>11</td>
</tr>
<tr>
<td>441</td>
<td>17</td>
<td>202</td>
</tr>
<tr>
<td>6</td>
<td>BC/UC &amp; Viral Panel negative</td>
<td>Rapid strep negative</td>
</tr>
</tbody>
</table>
Initial Management of SJS/TEN

- Requires early recognition
- Withdrawal of potential causative medication
- Supportive care
- Therapeutic interventions?

Initial Management

- FEN: IV fluids with D2 ½ NS @ 1.5 x maintenance
- NPO, stress ulcer prophylaxis
- Maintain UO > 1ml/kg/hr
- Determine % skin involvement
  - Parkland formula
  - 4 ml/kg/day per 1% BSA
  - 2 ml/kg/% BSA + maintenance
- Resp: Airway evaluation
- CV: PIVs
  - NS 20 ml/kg IV Bolus

- ID: Dc clindamycin, pancultured
- Imm: Dc solumedrol & start IVIG
- Neuro: pain control
- Skin: Specialty bed, minimize manipulation, monitor for hypothermia, bacitracin to open lesions
- Eyes: artificial tears, bacitracin ophthalmic oint.
- Consults: Dermatology, ENT, ophthalmology, pediatric surgery, wound team, PICC team, pain team, nutritionist, child life, SW
Case Study Progression

- Patient developed some WOB, mild hypoxia
- Placed on HFNC 40%, 10 L
- ENT consulted & elective Bronchoscopy & intubation
- Nasally intubated with 5.0 cuffed tube & sutured in place
- Laryngoscopy: supraglottis friable, mild airway edema, ulcerated epiglottis, vocal cords & distal trachea normal
- Skin: progressing lesions, blisters, & denuded skin
- Derm consult: skin biopsy

Specific Therapies: IVIG

- First pediatric case report by Amato in 1992
  - Can inhibit Fas-Fas ligand mediated apoptosis
- Uncontrolled clinical trials
  - Morici et al., 2000: 7 children given 2 gm/kg/total dose & 5 children supportive therapy only
    - Significant reduction in duration of fever in IVIG-treated group (8 vs. 14 days)
  - Metry et al., 2003: retrospectively analyzed 7 children treated with 2 gm/kg/total dose
    - No new blisters within 24-48 hr after initiation of treatment
    - Concluded high-dose IVIG appears effective in blocking the progression of SJS & reducing skin healing time
- Schneck et al., 2008: retrospectively compared 75/206 pts with/without IVIG
  - No significant benefit
  - Yang et al., 2009: retrospective 12/35 with/without IVIG
    - No significant reduction in mortality, time of progression & hospitalization

Specific Therapies: Corticosteroids

- Some benefit reported when patients treated before extension of rash (Kakourou et al., 1997)
- Prospective study in 16 children receiving corticosteroids vs. supportive care within 3 days of admission
  - Tx group had shortened duration of fever (4 vs. 9 days)
  - No significant reduction in eruption of rash
  - Minimal complications in both groups
Specific Therapies:
Corticosteroids

- Retrospective studies suggest increased morbidity
  - 32 children with SJS had ↑'d frequency of complications in those treated with corticosteroids (53% vs. 0%) (Rasmussen 1976)
  - 51 children with SJS had a complication rate of 74% in tx group vs. 28% in supportive care group (Ginsburg 1982)
  - 159 adults received corticosteroids vs. 122 supportive care. No significant benefit (Schneck et al, 2008)
  - 47 adults with vs. 18 supportive care, increased mortality seen in steroid group (Yang et al, 2009)

- Complications: infection, GI bleed, delayed wound healing

Specific Therapies:
Immodulation

- Removal of drug metabolites
- Plasmapheresis
  - Several case reports with 1-8 plasma exchanges
  - 8 consecutive pts with historical controls
  - No significant difference in mortality, LOS, or time to re-epithelialization (Furubacke et al 1999)
  - 5 pts – low mortality with combined IVIG & plasmapheresis (Lissa et al 2005)
- Cyclophosphamide
  - Most studies used concomitant corticosteroids
  - 8 pts with TEN received tx – all survived (Trautmann et al 1998)
- Cyclosporine
  - Retrospective comparative study (Arevalo et al 2000)
  - Safe & associated with a more rapid re-epithelialization rate & reduced mortality (0/11 vs. 3/6) than tx with cyclophosphamide & corticosteroids

Specific Therapies:
Hyperbaric Oxygen Treatment

- Improves oxygen delivery to the tissues
- Promotes sloughing of necrotic tissue
- Enhances dermal vascularization
- Activates epithelialization
- Ruocco et al 1986
  - 3 patients
  - 10 treatments
  - Re-epithelialization

Henry's Law:

Amount of ideal gas dissolved in solution
Is directly proportional to its partial pressure
Based on current evidence, there is insufficient data to support any of the proposed therapeutic interventions.

Global Management Goals

- **FEN:**
  - Correct electrolyte disturbances
  - Replace fluid losses
  - Meet high caloric needs with EN/PN
- **Respiratory:**
  - Maintain patent airway & adequate ventilation
- **CV:**
  - Maintain hemodynamic stability
  - IV access
- **ID:**
  - Prevent secondary infections
  - Aseptic care/foley
- **Wound/skin:**
  - Comprehensive/meticulous care to promote wound healing
  - Maintain thermoregulation
- **Neuro:**
  - Optimize pain management
- **Other:**
  - Prevent secondary complications
    - Oral/eye/skin/genital
  - Social:
    Patient/family counseling & support

Case Study Progression

- Rash continued to progress
  - % BSA involvement – 75% within 72 hr
- IVIG administered
  - 2 gm/kg over 48 hrs
- Wound management:
  - Overall blistering & sloughing of skin
  - No debridement
  - Cleansed with warm sterile water, mepilex Ag q day to torso & all ext
  - Aquacel Ag pm to buttocks, scrotum & penis
  - Burn sheets
  - Bacitracin/bactroban to face/ears
  - Orbase paste for oral lesions
  - Specialty bed
Critical Nursing Strategies: Wound Care

- Silver powered antimicrobial dressing
  - Examples: Acticoat, AQUACEL AG®
  - Hydro fiber technology
  - Indicated for mod to high exuding wounds
  - Infected or at risk

- Applied to open areas where skin sloughed: buttocks, scrotum & penis
  - Dressings changed QOD

Wound Care: Silver Impregnated Dressing

- Antimicrobial drsg that incorporates hydrofiber which releases ionic silver in controlled manner
- Locks bacteria in gelled fibers away from the wound bed
- Sustained activity for up to 7 days

Critical Nursing Strategies: Wound Care

- Foam drsg (i.e. Mepilex) applied to torso & extremities
  - Absorbs exudates
  - Minimizes risk of peri-wound skin maceration & erosion,
  - Waterproof
  - Provides bacterial protective barrier
- Wrapped with gauze
FEN Management
- Correct electrolyte disturbances & replace fluid losses
- IVF typically 1.5 X maintenance
- Serial electrolytes: required KCL & NaCL
- GI prophylaxis: zantac
- Initiate early enteral feeding if possible
  - Patient was started on postpyloric feeds on HD # 2
  - Goal ~150% of BEE
- Meet high metabolic demands
  - Monitor nutritional markers
  - Hypoalbuminemia – albumin replacement
- Consider supplementation to promote wound healing
  - Zinc
  - MVI
- Stool regimen initiated
  - Softener & stimulant

Respiratory Management
- Maintain patent airway
  - Consider elective intubation
- Mechanical ventilation
  - Pt was maintained in PRVC mode
  - FiO2 40% TV 180 (8 ml/kg), Peep 5, PS 10, Rate 16
- Aggressive pulmonary care

Cardiovascular Management
- Maintain hemodynamic stability
- Monitor for ongoing fluid losses
  - Epidermal detachment progresses over 3-5 days
- Adequate IV access
  - Avoid percutaneous central line if possible
  - Consider early placement of PICC for access
Infection Control Management

- Meticulous infection control & hygiene practices
- Prevent secondary infections, aseptic care
- Panculture with fever > 38.3
- Serial CBC, manual diff, & CRP
- Low threshold for initiation of broad spectrum antibiotics with suspicion of sepsis
  - Avoidance of β-lactam, carbapenems & monobactams

Critical Nursing Strategies: Comfort Measures

- Continuous Fentanyl & Versed infusions
  - SBS & FLACC assessment tools
- Ketamine prn
  - Dressing changes/eye exams
- Prolonged intubation secondary to airway obstruction
  - Enteral Methadone/Valium initiated
- Dexmedetomidine infusion
  - Transition off continuous narcotic/benzodiazepine infusions
  - Preparation for extubation

Critical Nursing Strategies: Eye Care

- Artificial tears to both eyes q 1 hr
- Ophthalmology Exam:
  - Significant eye drainage
  - No pseudomembrane
  - Bacitracin ophthalmic & artificial tears
  - Eyes kept closed between applications
  - Steroid ointment
  - Ophthalmology exams q 2 days under sedation
    - Developed mild chemosis & corneal abrasions
    - Steroid oint dcd
    - Ciloxan QID started
Critical Nursing Strategies: 
Mouth and Lip Care

- Magic Mouth Wash/orabase topical
- Sutured endotracheal tube
  - Vomer stitch
  - Xeroform drg prevent scabbing
- Biting on endotracheal tube
  - Bite block placed
- Scabbing
  - Easily dislodged
  - Excessive bleeding
  - Amicar soaked gauzes

Basic Nursing Care Challenges

-Rooney & Poolacheria, 2010; Burns

Case Progression

- Persistent daily fevers
- HD # 5 Fever to 38.9, HR 150s, Bp 60s/40
- Pancultured
- WBC 4.2, 16% bands
- Fluid resuscitated
- Dopamine infusion
- Arterial line placed
- Broad spectrum antibiotics
  - What to use?
Case Progression

- Cx remained negative
- Antibiotics dc'd after 72 hrs
- Improving skin:
  - Re-epithelialization of skin
- Wound care changed
  - Hydroform cream to areas with sloughing of dead epidermis
  - Adaptic with biafine cream to face, ears, & penis
- Extubated in OR ~ 1 month after admission

Case Progression

- Speech consult after extubation
  - MBS
    - Delayed swallowing, no laryngeal penetration or aspiration
- Narcotic/benzo tolerance/withdrawal
- Skin: hypopigmented areas, minimal scarring
- OT/PT rehabilitation
- Transitioned to rehab center on HD # 38

Critical Pearls

*Meticulous nursing care measures can potentially prevent serious long-term complications and include:*

- Aggressive eye care
- Comprehensive skin care regimen
- Aggressive pain management & comfort
- Rigid compliance with infection control measures
References