Necrotizing Soft Tissue Infections

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Innoculation
- Soft tissue injury
- Wounds from contaminated abdominal, pelvic or perineal operations
- Unsterile injection by drug users
- Human, animal or insect bites
- Occult necessitating infections (diverticulitis)

Spread of Infection
- Diabetes mellitus
- Immunosuppression
- Chronic debilitating diseases
- Advanced age
- Malnutrition
- Ischemia
- Inadequate debridement of infection
Presenting Signs of NSTI

<table>
<thead>
<tr>
<th>Sign</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>100</td>
</tr>
<tr>
<td>Erythema</td>
<td>77</td>
</tr>
<tr>
<td>Induration</td>
<td>43</td>
</tr>
<tr>
<td>Swelling</td>
<td>20</td>
</tr>
<tr>
<td>Fluctuant</td>
<td>20</td>
</tr>
<tr>
<td>Necrosis</td>
<td>10</td>
</tr>
<tr>
<td>Bullae</td>
<td>3</td>
</tr>
<tr>
<td>Crepitance</td>
<td>3</td>
</tr>
</tbody>
</table>

33 patients SFGH
illicit drug use prevalent


Diagnostic Radiology

- All modalities have been utilized
  - Tissue gas, edema & induration
  - Deep abscess and fluid collections

- Confirmatory evidence
  - When pain is only presenting symptom
  - Should not delay surgery

Objective Criteria

- 21 cases of NTSI paired with matched non-NTSI controls
- Univariate and multivariate analysis
  - Lab results
- Elevate WBC > 14 x 10^9/L
- Serum sodium <135 mmol/L
- BUN > 15mg/dL
- Mortality predicted by WBC > 30 x 10^9/L
- Transfer from other facilities prior to definitive care had a higher mortality


Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Cutoff</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive Protein (mg/L)</td>
<td>&lt; 150</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥ 150</td>
<td>4</td>
</tr>
<tr>
<td>WBC (per mm³)</td>
<td>&lt; 15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>15-25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt; 25</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&gt; 13.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-13.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt; 11</td>
<td>2</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>≥ 135</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 135</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>≤ 141</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 141</td>
<td>2</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>≤ 10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>1</td>
</tr>
</tbody>
</table>

13 possible > 6 suggestive ≥ 8 predictive

Bacteriology

- Incidence of mixed infections varies from 30-60%
  - Highly depends on reliability of culture handling
  - Synergism is suspected but not well documented
- Tissue Gram stain very reliable

Virulence Factors

- Bacterial-derived enzymes
  - Microvascular thrombosis
  - Areolar tissue degradation
  - Antibiotic resistance
- Systemic responses
  - Induce pro-inflammatory cytokines
    - Endo- and exotoxins

Fournier's Gangrene

- Serious perineal infections
  - Urogenital or rectal contamination
  - May extend into pelvis, thigh or abdominal wall
- Highly associated with diabetes
- May require secondary fecal or urinary diversion

Clostridial Prone Wounds
Pathophysiology of Clostridial Myonecrosis

- Entry of \textit{C. perfringens} type A spores or vegetative cells
  - Surgical wounds
  - Traumatic injury
- Originate from soil, GI contamination, parenteral drug injection
- Local tissue ischemia and anaerobic conditions
  - Facilitates germination of spores

\textit{C. perfringens} Genome

- Extracellular toxins and enzymes
  - Known virulence-related genes
    - α, β, θ, κ, ε, ι, μ−toxins
  - 4 enterotoxins similar to \textit{B. cereus}
  - 5 hemolysins
  - A collagen adhesin similar to \textit{S. aureus}
  - 2 fibronectin-binding proteins similar to \textit{B. subtilis} and \textit{L. monocytogenes}
  - Cysteine proteinase (α-clostripain)
  - 5 hyaluronidases
  - VirS/VirR regulatory system
    - Sensor histidine kinases

Clostridial Myonecrosis

San Francisco General Hospital

- Black Tar Heroin
- Five injection drug users sustained necrotizing soft tissue infections
  - 3 roommates
  - One shared needles/metamphetamine user
  - One obtained drugs from same “dealer”
- Molecular epidemiologic study
  - Pulsed field gel electrophoresis of SmaI restriction digests performed

Investigated Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Outcome</th>
<th>Source</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Died</td>
<td>R flank</td>
<td>\textit{NG}</td>
</tr>
<tr>
<td>2</td>
<td>Died</td>
<td>R flank</td>
<td>\textit{C. sordellii}</td>
</tr>
<tr>
<td>3</td>
<td>D/C</td>
<td>R flank/thigh</td>
<td>\textit{C. perfringens}</td>
</tr>
<tr>
<td>4</td>
<td>Amputation</td>
<td>R forearm</td>
<td>\textit{C. perfringens}</td>
</tr>
<tr>
<td>5</td>
<td>D/C</td>
<td>L hip</td>
<td>Group F Strep</td>
</tr>
<tr>
<td>6</td>
<td>D/C</td>
<td>R upper arm</td>
<td>Group F Strep, other oral flora</td>
</tr>
<tr>
<td>7</td>
<td>D/C</td>
<td>L shoulder</td>
<td>\textit{C. sordellii}</td>
</tr>
<tr>
<td>8</td>
<td>D/C</td>
<td>R forearm</td>
<td>\textit{C. perfringens} (abscess)</td>
</tr>
<tr>
<td>9</td>
<td>D/C</td>
<td>Blood</td>
<td>\textit{C. perfringens} (contaminant)</td>
</tr>
</tbody>
</table>

\textit{Bansberg et al., Arch Int Med} 162:517 ’02
Environmental Cultures

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clone</th>
<th>Patient Samples</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>C perfringens</td>
<td>A1</td>
<td>Case 3 (roommate)</td>
<td>Syringe 1</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>Case 4 (met user)</td>
<td>Spoon 1, penknife, blade</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Case 4</td>
<td>Spoon 1</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Case 5</td>
<td>Spoon 1</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td></td>
<td>Spoon 2</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td></td>
<td>Spoon 1</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Heroin, Case 2</td>
<td>Spoon 3</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td></td>
<td>Roofi teces</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td></td>
<td>Toilet water</td>
</tr>
<tr>
<td>C sordellii</td>
<td>A</td>
<td>Case 2 (roommate)</td>
<td>Spoon 2</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Case 5</td>
<td>Spoon 2</td>
</tr>
</tbody>
</table>

Group A Streptococcus

- Streptococcal toxic shock
  - Early coagulopathy, renal failure and hypoxia
  - Virulent strains cycle ~ 10 years
- High incidence of medical staff exposure and contamination
  - Pharyngitis
- “Flesh-eating” bacteria
- Occasionally occult inoculation

Erysipelas

Group A Strep

- Image of Erysipelas
- Image of Group A Strep
Ambulatory Treatment of Soft Tissue Infections

SFGH ISIS Clinic: 2.5 yrs

- 12012 infections in 6156 pts
- 84% homeless
- 58% illicit parenteral drug use
- *Staph aureus* isolated in 83%
  - MRSA was 76%


### MRSA

<table>
<thead>
<tr>
<th>At risk</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, athletes, inmates, soldiers, IVDA, SAHM</td>
<td>Long term care, diabetics, dialysis and prolonged hospitalization</td>
<td></td>
</tr>
<tr>
<td>SCCmec type</td>
<td>IV</td>
<td>I, II and III</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>B-lactam alone, common, usually responds to TMP/SMX</td>
<td>Multidrug, common, usually responds to TMP/SMX</td>
</tr>
<tr>
<td>PVL toxin</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Assoc Syndromes</td>
<td>SSTI, postinfluenza necrotizing pneumonia</td>
<td>nosocomial pneumonia, Catheter-related UTI, bloodstream infection, SSIs</td>
</tr>
</tbody>
</table>


### Spider Bite CA-MRSA

Harbor-UCLA

- 14/843 patients (2003-04) with necrotizing fasciitis, necrotizing myositis, or both
- Median age 46 years (range 28-68) and 71 % men
- Coexisting conditions
  - Current or past injection-drug use (43 percent)
  - Previous MRSA infection, diabetes, and chronic hepatitis C (21 percent each)
  - Pancer, HIV or AIDS (7 percent each)
  - Four none (29 percent)
- Combined medical and surgical therapy
  - none died
  - serious complications, including the need for reconstructive surgery
- 86 % percent monmicrobial for MRSA
  - 40 % had positive results
- All isolates susceptible in vitro to clindamycin, bacitracin, and rifampin
- Genotype: all type ST8, USA300, SCCmecIV and carried the Panton-Valentine leukocidin (pvl), lukD, and lukE genes


### Necrotizing Infections Caused by CA-MRSA

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Importance of Panton-Valentine Leukocidin in CA-MRSA

Left: lung from rabbit infected with CA MRSA
Right: lung from rabbit infected with CA MRSA without the bacterial toxin PVL


Initial Management of Serious Necrotizing Infections

- Blood and wound cultures
- Administration of antibiotics
- Operative debridement
- Adjuncts
  - Hyperbaric oxygen
  - Activated protein C
  - IV IgG

Inappropriate Antimicrobial Therapy: Prevalence among Intensive Care Patients


- Empiric Antibiotics
  - Vancomycin
  - Ceftriaxone
  - Clindamycin or metronidazole
- Specific antibiotics
  - Penicillin

Antibiotics
**Alpha-toxin Production**

*C. perfringens* Co-culture with Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Alpha-toxin Activity (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min 0 15 30 45 60</td>
</tr>
<tr>
<td>None</td>
<td>90 100 100 120 140</td>
</tr>
<tr>
<td>Penicillin</td>
<td>90 80 80 100 90</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90 0 0 0 0</td>
</tr>
<tr>
<td>Rifampin</td>
<td>90 0 0 0 0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>90 0 0 0 0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>90 0 0 0 0</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>90 0 0 0 0</td>
</tr>
</tbody>
</table>


**Operative Debridement**

- Resect to level of bleeding tissue
- Amputation
- Avoid surgeon injury from broken needles
- Gram stain the tissue margins
- Early re-examination of the wound in 6-12 hrs

**Buttock Wound with Necrosis**

**Toxic Shock Syndrome Diagnostic Criteria**

- Hypotension< 90 mmHg
- Diffuse Erythematous rash
- Desquamation of rash 1-2 weeks later, palms soles
- Organ Failure
  - GI: vomiting, hyperemic mucosa
  - Myalgia: CPK elevation
  - Renal: Cr x2
  - Coagulopathy: Platlets <100,000/mm²
- Neurological changes
- Toxic shock syndrome toxin (TSST-1)
Case History

- 34 yo F IDU
- R thigh pain and erythema, WBC 34K
- OR debridement
- *C perfringens* cultured
- 4 hr post-op: PO 54 with FIO 1.0 and 14 PEEP, BE -14.3 mEq/L
- 8 hr Rx Activ Prot C
- 36 hr post-op: resolution of hypoxia and acidosis
- Full recovery

Hyperbaric Oxygen (HBO)

- First report of efficacy
  - Brummelkamp '61 (Netherlands)
  - 2-2.5 ATA
- HBO suppresses \(\alpha\)-toxin production
  - Van Unnick '65
- Risks
  - Oxygen toxicity, decompression sickness, middle ear damage

Analysis of Mortality

SFGH 1990-98

- 10 patients admitted awake and alert
  - Complaint of pain at infection site
  - All illicit parenteral drug use
  - Average syst BP > 95
  - Average WBC > 35 K
  - Skin changes were rare
- Standard fluid resuscitation

Mortality Analysis

Hospital Length of Stay
**Analysis of Mortality**

Average Fluid Infusion

- Pre-Op
- Intra-Op
- Post-Op

<table>
<thead>
<tr>
<th>Location, Yr</th>
<th>n</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York, '93</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Cleveland, '95</td>
<td>65</td>
<td>29</td>
</tr>
<tr>
<td>Oakland, '96</td>
<td>45</td>
<td>27</td>
</tr>
<tr>
<td>San Francisco, '98</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Shreveport, '98</td>
<td>68</td>
<td>15</td>
</tr>
<tr>
<td>Ann Arbor, '00</td>
<td>37</td>
<td>24</td>
</tr>
<tr>
<td>India, '02</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>Los Angeles, '04</td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td>Seattle, '05</td>
<td>166</td>
<td>17</td>
</tr>
</tbody>
</table>

**Critical Care Management**

- Intravenous fluids
  - Massive tissue edema
  - Resolve acidosis
- Avoid $\alpha$-adrenergic pressors
  - Produce tissue ischemia
- Correction of DIC
- Mechanical ventilation
  - ARDS protocol

**Mortality**