Necrotizing Soft Tissue Infections: Delays in Treatment

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PS321: Necrotizing Soft Tissue Infections: Time Matters
Wednesday October 7, 2015
60 yo female with DM and HTN

Presents to ED ~36 hours after repair of contaminated LE laceration
- 10/10 pain
- LE swelling, erythema, ecchymosis
- Vitals: temp 98, HR 110, BP 107/76

1 hour after presentation
- Labs: WBC 13.8, HCT 50, Na 131, CO2 18, Glucose 348, Creat 2.05
- Plain X-ray: gas in tissue
- Broad spectrum IV antibiotics given

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
60 yo female with DM and HTN

3 hrs after presentation - admit to OBSERVATION
   – Admission diagnosis: CELLULITIS
   – Bullous lesions documented

7.5 hrs after presentation – transferred to higher level of care

9.5 hrs after presentation – AKA

Died after several weeks in the hospital
Time to Treatment Matters

Courtesy of American College of Surgeons Division of Education
Clinical Congress 2015
Disclosures:

• Receive research funding and consultant for AtoxBio

• Research funding from several pharmaceutical companies

• No significant conflicts to disclose for this presentation
Infectious and inflammatory stimuli develop in non-linear fashion

- The effects are not simply additive – geometric or exponential
- The greater the degree of cellular dysfunction, the more difficult to repair/correct injury
- Intervene before severe dysfunction develops

![Graph showing the relationship between Degree of cellular dysfunction and % Mortality](image)

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Simplified Model of Oxidant Stress in Sepsis, Shock, and Trauma

- Infection
  - PAMPs
  - DAMPs

- Tissue trauma, injury, & damage
- Shock & Ischemia/Reperfusion
  - Loss of antioxidant potential

- Innate immune system activation
- Inducible Nitric Oxide Synthetase
- Xanthine oxidase generation

- Oxidative injury to membranes, proteins, chromosomes

- Mitochondrial oxidant injury & Cytopathic hypoxia
- NF-κB activation
- Cytokines Chemokines

- ATP
- HOCl
- ONOO⁻
- \( \cdot \text{NO} \)
- \( \cdot \text{O}_2 \)
- \( \cdot \text{OH} \)
- hypoxanthine

- \( \text{O}_2^- \)
- \( \text{xanthine} \)
- \( \text{O}_2 \)

- \( \text{ONOO}^- \)

- Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Mortality from NSTI is declining!

<table>
<thead>
<tr>
<th>Publication date:</th>
<th>Number of studies</th>
<th>Number of Cases</th>
<th>Number of deaths</th>
<th>Percent Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980 through 1990</td>
<td>17</td>
<td>375</td>
<td>119</td>
<td>31.7%</td>
</tr>
<tr>
<td>1991 through 2000</td>
<td>15</td>
<td>628</td>
<td>167</td>
<td>26.6%</td>
</tr>
<tr>
<td>2001 through 2010</td>
<td>37</td>
<td>2670</td>
<td>565</td>
<td>21.2%</td>
</tr>
<tr>
<td>2011 thought 2014</td>
<td>11</td>
<td>2508</td>
<td>394</td>
<td>15.7%</td>
</tr>
<tr>
<td>Total 1980 - 2014</td>
<td>80</td>
<td>6181</td>
<td>1245</td>
<td>20.1%</td>
</tr>
</tbody>
</table>

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Treatment of NSTI

1. Resuscitation

2. Antibiotic therapy

3. Surgical debridement – source control

*Time to achieve each one matters!*
Time to Resuscitation Matters

• Goal of resuscitation is the restoration of tissue perfusion and elimination of cellular hypoxia
Use of Early Goal Targeted Resuscitation

Rivers, E. *NEJM* 2001;345:1368-77
Use of Early Goal Targeted Resuscitation

NNT to prevent 1 event (death) = 6-8

<table>
<thead>
<tr>
<th></th>
<th>Standard therapy</th>
<th>EGDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>60-day mortality</td>
<td>50%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Rivers, E. *NEJM* 2001;345:1368-77

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Time to Resuscitation Matters

Surviving Sepsis Campaign  Resuscitation Bundle

- Serum lactate measured.
- Blood cultures obtained prior to antibiotic administration.
- Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
- In the event of hypotension and/or lactate $\geq 4$ mmol/L:
  - Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent)
  - Initiate vasopressor for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $\geq 65$ mmHg
- Achieve central venous pressure (CVP) of $\geq 8$ mmHg
- Achieve central venous oxygen saturation $\text{ScvO}_2 \geq 70\%$ or a mixed venous oxygen saturation ($\text{SvO}_2 \geq 65\%$).

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Before implementing SSC-RB:

- Patients in septic shock: 96
- Mortality from sepsis: 57.3%

After implementing SSC-RB:

- Patients in septic shock: 384
- Mortality from sepsis: 37.5%

Regression model for risk of death: OR 0.5 (0.28-0.89)

Compliance with six + components by 6 hrs: OR 0.3 (0.17-0.53)

ScvO2 >70% by 6 hrs: OR 0.62 (0.38-0.99)
• Retrospective analysis – 594 pts with severe sepsis and septic shock

• Treatment directed by the SSC – RB

• Greater fluid administration in the 1\textsuperscript{st} 3 hours in SURVIVORS

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non-survivors</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} 3 hrs: 2,085 ml</td>
<td></td>
<td>1,600 ml</td>
<td>0.007</td>
</tr>
<tr>
<td>2\textsuperscript{nd} 3 hrs: 660 ml</td>
<td></td>
<td>800 ml</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Multivariate analysis: age, weight, SOFA, APACHE III, total fluid in 6 hrs

➢ higher fluid in 1\textsuperscript{st} 3 hrs vs 2\textsuperscript{nd} 3 hrs – OR 0.34 (0.15 – 0.75)
Metaanalysis of Quantitative Resuscitation in Sepsis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Overall Mortality (%)</th>
<th>Mortality Timing</th>
<th>Study Location</th>
<th>Patient Selection</th>
<th>Concealment</th>
<th>Jadad Score</th>
<th>Intervention Timing</th>
<th>Group End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td>2006</td>
<td>224</td>
<td>61</td>
<td>Hospital</td>
<td>ICU</td>
<td>A</td>
<td>A</td>
<td>2</td>
<td>Early</td>
<td>CVP, MAP, UO</td>
</tr>
<tr>
<td>Rivers</td>
<td>2001</td>
<td>263</td>
<td>37</td>
<td>Hospital</td>
<td>ED</td>
<td>A</td>
<td>A</td>
<td>4</td>
<td>Early</td>
<td>ScvO₂</td>
</tr>
<tr>
<td>Alia</td>
<td>1999</td>
<td>63</td>
<td>70</td>
<td>ICU</td>
<td>ICU</td>
<td>A</td>
<td>A</td>
<td>1</td>
<td>Early</td>
<td>DO₂</td>
</tr>
<tr>
<td>Yu</td>
<td>1998</td>
<td>87</td>
<td>34</td>
<td>ICU</td>
<td>ICU</td>
<td>A</td>
<td>C</td>
<td>1</td>
<td>Early</td>
<td>DO₂</td>
</tr>
<tr>
<td>Yu</td>
<td>1993</td>
<td>52</td>
<td>19</td>
<td>30 day</td>
<td>ICU</td>
<td>A</td>
<td>B</td>
<td>1</td>
<td>Early</td>
<td>CI</td>
</tr>
<tr>
<td>Tuchschmidt</td>
<td>1992</td>
<td>51</td>
<td>61</td>
<td>14 day</td>
<td>ICU</td>
<td>A</td>
<td>C</td>
<td>2</td>
<td>Early</td>
<td></td>
</tr>
</tbody>
</table>

**Review:** Quantitative Resuscitation Strategy for Sepsis  
**Comparison:** 01 Quantitative Resuscitation vs. Standard Care  
**Outcome:** 01 Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (random) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Early</td>
<td>58/108</td>
<td>83/116</td>
<td>0.46 [0.27, 0.80]</td>
<td>A</td>
</tr>
<tr>
<td>Rivers 2001</td>
<td>38/130</td>
<td>59/133</td>
<td>0.52 [0.31, 0.86]</td>
<td>A</td>
</tr>
<tr>
<td>Alia 1999</td>
<td>23/31</td>
<td>21/32</td>
<td>1.51 [0.51, 4.46]</td>
<td>A</td>
</tr>
<tr>
<td>Yu 1998</td>
<td>15/58</td>
<td>15/29</td>
<td>0.33 [0.13, 0.83]</td>
<td>C</td>
</tr>
<tr>
<td>Yu 1993</td>
<td>4/30</td>
<td>6/22</td>
<td>0.41 [0.10, 1.68]</td>
<td>B</td>
</tr>
<tr>
<td>Tuchschmidt 1992</td>
<td>13/26</td>
<td>18/25</td>
<td>0.39 [0.12, 1.24]</td>
<td>C</td>
</tr>
<tr>
<td>Subtotal</td>
<td>383</td>
<td>357</td>
<td>0.50 [0.37, 0.69]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 151 (Treatment), 202 (Control)  
Test for heterogeneity: Chi² = 5.12, df = 5 (P = 0.40), I² = 2.4%  
Test for overall effect: Z = 4.25 (P < 0.0001)

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Treatment of NSTI

1. Resuscitation

2. Antibiotic therapy

3. Surgical debridement – source control
# Time to the RIGHT Antibiotic Matters

**Influence of Inadequate Empiric Antibiotic Therapy**

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Relative increase in mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kollef</td>
<td>Mixed nosocomial ICU infections</td>
<td>133%</td>
</tr>
<tr>
<td>Luna</td>
<td>Ventilator associated pneumonia</td>
<td>139%</td>
</tr>
<tr>
<td>Alvarez-Lerma</td>
<td>Ventilator associated pneumonia</td>
<td>56%</td>
</tr>
<tr>
<td>Rello</td>
<td>Ventilator associated pneumonia</td>
<td>131%</td>
</tr>
<tr>
<td>Leibovici</td>
<td>Bloodstream infection</td>
<td>70%</td>
</tr>
<tr>
<td>Ibrahim</td>
<td>Bloodstream infection</td>
<td>121%</td>
</tr>
<tr>
<td>Mosdell</td>
<td>Intraabdominal infection</td>
<td>110%</td>
</tr>
<tr>
<td>Burke</td>
<td>Intraabdominal infection</td>
<td>192%</td>
</tr>
<tr>
<td>Montravers</td>
<td>Nosocomial intrabdominal infection</td>
<td>92%</td>
</tr>
</tbody>
</table>

*Courtesy of American College of Surgeons Division of Education Clinical Congress 2015*
Time to Antibiotic Therapy Matters

- 2731 pts with septic shock (56% mortality)
- Time to AB Rx most strongly associated with outcome
- Each 1 hr delay → 12% increase in risk of death

Kumar A. CCM. 2006; 34:1589-1595

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Resuscitation and Antibiotics Cannot Replace Surgical Source Control
Time to surgical debridement matters!

Predictors of mortality by regression analysis in NSTI:

- Time to first debridement
- Extent of tissue involvement
- # Failed organs on admission
- Inadequate first debridement
- Age > 60 years
- Bacteremia
- Elevated lactate

Bosshardt TL. Arch Surg. 1996;131:846-52
Elliott DC. Ann Surg. 1996; 224:672-83
Bilton BD. Am Surg. 1998; 64:397-400

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Time from admission to OR matters:

- Time from admission to OR independently associated with mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Finding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lille</td>
<td>1996</td>
<td>&gt; 24 hrs increased mortality</td>
</tr>
<tr>
<td>Elliott</td>
<td>1996</td>
<td>OR 1.27 - days admit to debridement</td>
</tr>
<tr>
<td>Wong</td>
<td>2003</td>
<td>RR 9.4 - &gt; 24 hrs</td>
</tr>
<tr>
<td>Liu</td>
<td>2005</td>
<td>&gt; 24 hrs increased mortality</td>
</tr>
<tr>
<td>Golper</td>
<td>2007</td>
<td>OR 5.32 - &gt; 24 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR 2.18 - &lt; 12 hrs vs &gt; 24 hrs (p=0.07)</td>
</tr>
</tbody>
</table>
Does time always matter?

Studies where time from admission to OR is not associated with mortality

– Anaya 2005
– Hsiao 2008
– Gunter 2008
NSTIs: a heterogenous group of infections!

Type 1: polymicrobial
- typically arise from a chronic, indolent source
- spread along fascial planes
- most common ~ 50-75% of NSTIs

Type 2: monomicrobial virulent Gm +, aerobic cocci
- Streptococcus species
- CA-MRSA
- pathophysiology related to toxin production

Type 3: monomicrobial virulent Gm + or Gm – bacilli
- Clostridia species
- Bacillus species
- Vibrio species
- Aeromonas species
- Eikenella species
- pathophysiology related to toxin production and growth rate of pathogens

Rapidly progressive

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015
Highly virulent pathogens associated with increased mortality:

• **Group A strep** *(Childers-2002, Golper 2007)*
  – Gram positive antiribosomal agent - Clindamycin

• **Clostridia** *(Anaya-2005)*
  – Gram positive antiribosomal agent - Clindamycin

• **Aeromonas and Vibrio** *(Hsiao-2008)*
  – Gram negative antiribosomal agent – tetracycline class
Time to OR decreasing over time

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Cases</th>
<th>Mortality</th>
<th>Hours from admission to OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>McHenry</td>
<td>1995</td>
<td>65</td>
<td>29%</td>
<td>40 hours</td>
</tr>
<tr>
<td>Elliott</td>
<td>1996</td>
<td>198</td>
<td>25%</td>
<td>41 hours</td>
</tr>
<tr>
<td>Anaya</td>
<td>2005</td>
<td>166</td>
<td>17%</td>
<td>23 hours</td>
</tr>
<tr>
<td>Hsiao</td>
<td>2008</td>
<td>128</td>
<td>19%</td>
<td>60 hours</td>
</tr>
<tr>
<td>Gunter</td>
<td>2008</td>
<td>52</td>
<td>10%</td>
<td>9 hours</td>
</tr>
</tbody>
</table>

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Does time to re-debridement matter?

- 64 patients with NSTI at USC-LAC over 6 years
- Practice algorithms by 2 different services
  - Short duration (24-48 hrs) vs Extended duration (> 48 hrs) until second debridement
- Short duration associated with lower AKI and mortality

<table>
<thead>
<tr>
<th>Table 4. Comparison of Outcomes in Patients with Necrotizing Soft Tissue Infection Subjected to SIRD vs EIRD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (n = 64)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>ICU admission</td>
</tr>
<tr>
<td>Operative débridements; mean ± SEM</td>
</tr>
<tr>
<td>ICU LOS (days); mean ± SEM</td>
</tr>
<tr>
<td>HLOS (days); mean ± SEM</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
<tr>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>Other†</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

Courtesy of American College of Surgeons Division of Education Clinical Congress 2015

Treatment of NSTI: TIME MATTERS

1. Resuscitation

2. Antibiotic therapy

3. Surgical debridement – source control

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Thank you for your attention