Update on Surviving Sepsis 2008
Objectives

- Epidemiology of Sepsis
- Definition of Sepsis and Septic Shock
- Review Guidelines for Resuscitation
  - Dx: Lactate, cultures, SVO2
  - Tx: EGDT, timing/choice of abx, activated protein C
Epidemiology

• In the U.S. Annually:
  – Incidence of Sepsis 750,000
    • 160,000 (~20%) are surgical patients
  – 30-40% mortality despite abx and source control
    • ~250,000 deaths per year
  – Cost $17 Billion

Epidemiology

• Compared to medical septic pts, surgical pts:
  – LOS + 7 days
  – Cost +$10,000

• Compared to non-septic surgical pts:
  – Cost 5x higher

Angus, Crit Care Med 2001; 29:1303
Importance of Severe Sepsis: Comparison With Other Major Diseases

Incidence of Severe Sepsis

Mortality of Severe Sepsis

Determinants of Mortality

- Source control is most vital factor
- Resuscitation/re-establish perfusion in 6 hrs
- Appropriate IV abx in 1 hr
Systemic Inflammatory Response Syndrome (SIRS)

- Inflammatory response that includes 2 or more of the following:
  - Temp > 38ºC or < 36 ºC
  - HR > 90/min
  - RR > 20/min or PaCO2 < 32 mmHg
  - WBC > 12K, <4K, or > 10% bands

- Sepsis: SIRS + Infection
Severe Sepsis

• Sepsis with end-organ dysfunction
  – Oliguria
  – Increase Creatinine
  – Altered mental status
  – Elevated Lactate
Septic Shock

- Sepsis with hypotension despite adequate fluid resuscitation (20 ml/kg)
  - SBP < 90 or MAP < 70
  - In hypertensive pts, SBP decrease > 40mm Hg from baseline
Definition Summary

- **SIRS**: HR $> 90$, RR $> 20$, $12 < \text{WBC} < 4$, $38 < \text{temp} < 36$
- **Sepsis**: SIRS + Infection
- **Severe Sepsis**: Sepsis + organ dysfunction
- **Septic Shock**: Sepsis + hypotension
Pathophysiology

• Distributive shock state
  – Vasodilation of arterioles – low SVR, low BP
    • Compensate with tachycardia and elevated CO/CI
  – Pre-capillary A-V shunts
    • Low BP – bypass capillary resistance beds
    • Elevated SVO2
    • Elevated lactate
Pathophysiology

• Classic physiologic derangements most associated with LPS
• Can be associated with exotoxin from gram positive bacteria or large gram positive load
• Least associated with fungemia (atypical symptoms)
Diagnosing the Septic Pt

• Combine clinical exam and labs/imaging
  – Elderly
    • Can’t mount a fever or leukocytosis
    • Ability to develop bandemia preserved
  – Immunosuppressed/steroids
Diagnosing Sepsis

- Lab tests: CBC, Chem, CULTURES, lactate, SVO2
  - SVO2 is a measure of O2 extraction (NL 70%)
    - **UNDER-RESUSCITATED** septic pts have a LOW SVO2
    - **RESUSCITATED** septic pts have a HIGH SVO2
  - Lactate is a measure of the severity of sepsis
    - Lactate > 4 that does not correct in 6 hrs is bad
Treatment

- Based on Early Goal Directed Therapy
- Very broad, high dose, rapid administration of iv abx
- Consider Activated Protein C
- Minimal role for steroids

N=230
9% Surgical

Rivers, NEJM 2001; 345:1368
Treatment

Comparative Mortality Reductions

Absolute Risk Reduction
Treatment

Start with 1-4 liter bolus of saline or LR

– Elevated lactate is not a contraindication to LR
– Pressor if needed to temporize while fluids are running or if unresponsive to fluids alone
Treatment – Fluid Choice

• Colloid (Hespan)
  – Starch polymer that cannot cross cap endothelium in non-inflammed state
  – Mild anti-platelet effects after 1.5-2 liters/day
  – Possible adverse effect on renal function

• Albumin (SAFE Trial)*
  – No difference between Albumin and saline
  – Possibly worse in trauma, esp TBI
  – Excluded liver and burn pts

*NEJM 2004; 350:2247
Treatment – Choice of Fluids

• FFP – “We recommend FFP not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned operation”*

Surviving sepsis campaign 2008
Percent of Patients with Any New Infection

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>FFP Transfused</th>
<th>No FFP Transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP N=380</td>
<td>8</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>No FFP N=2058</td>
<td>6</td>
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<td></td>
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</table>

Sarani Critical Care Med 2008; 36:1114
## FFP Study (HUP)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.994</td>
<td>0.98-1.005</td>
<td>0.27</td>
</tr>
<tr>
<td>FFP</td>
<td>1.039</td>
<td>1.013-1.067</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RBC</td>
<td>1.074</td>
<td>1.043-1.107</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1.126</td>
<td>1.102-1.152</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Sarani Critical Care Med 2008; 36:1114
Treatment - Fluids

• Endpoints of therapy
  – MAP > 65 mm Hg, HR < 100 bpm
  – UOP > 0.5 cc/kg/hr
  – SVO2 70% or more
  – CVP > 10-15
    • Higher if known cardiomegaly or intubated
  – TTE showing cardiac filling
  – Until you no longer see improvement in hemodynamics following boluses (concept of volume-responsiveness)
## Treatment - Vasopressors

<table>
<thead>
<tr>
<th></th>
<th>DA-R (↑UOP)</th>
<th>B₁ (↑ HR)</th>
<th>B₂ (↓BP)</th>
<th>α₁ (↑ BP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td>1-5 mcg/kg/min</td>
<td>6-10 mcg/kg/min</td>
<td>&gt;10 mcg/kg/min</td>
</tr>
<tr>
<td>1-15 mcg/kg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phenylephrine</strong> (Neosymphephrine)</td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>1-300 mcg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Norepinephrine</strong> (Levophed)</td>
<td>+</td>
<td></td>
<td></td>
<td>++++</td>
</tr>
<tr>
<td>1-20 mcg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epinephrine</strong> (God’s Pressor)</td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>1-10 mcg/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dobutamine</strong> (1-10 mcg/kg/min)</td>
<td>++++</td>
<td>++</td>
<td></td>
<td></td>
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<tr>
<td><strong>Milrinone</strong> (0.125-0.5 mcg/kg/min)</td>
<td>++++</td>
<td>+++</td>
<td></td>
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</table>

Potency + scale is from 1-4
Treatment

• Blood Transfusion
  – Rivers’ trial transfused for Hg < 10 if SVO2 remained low after IVF and after MAP > 65
  – Role for pre-emptive transfusion?
    • e.g. Hg 10-11 with elevated lactate/shock
    • Time to replete 2,3 DPG, good colloid resuscitant
    • Immunosuppressive
# O2 Delivery in Sepsis

<table>
<thead>
<tr>
<th>Author, Year, Journal</th>
<th>Population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietrich 1990 Crit Care Med</td>
<td>N= 32, MICU, septic, RCT</td>
<td>Hg 8→10.5, no change in PAOP, CI, lactate, SVO2</td>
</tr>
<tr>
<td>Lorente 1993 Crit Care Med</td>
<td>N=16, MICU, septic, RCT</td>
<td>Dobutamine increases SVO2 but RBC does not</td>
</tr>
<tr>
<td>Fernandes 2001 Crit Care</td>
<td>N=15, MICU, septic, RCT</td>
<td>RBC does not change gastric tonometry or lactate</td>
</tr>
</tbody>
</table>
Treatment – Source Control

• Imaging
  – Consider U/S if too unstable to travel
  – Bedside percutaneous interventions/drains

• Conditions with 100% mortality if not operated on quickly
  – Nec fasciitis, non-sealed perforated viscus
Treatment – IV Abx

• Mortality increases 7% for every hour delay in antibiotic administration*

*Sepseis Bundle at HUP

Sunrise

*Kumar A. Crit Care Med 2006; 34: 1589-96
**Sepsis Algorithm:**

**Empiric Antimicrobial Selection**

- **DRAW BLOOD CULTURES, LACTATE, VENOUS BLOOD GAS**
  - Has the patient received therapy with a late generation cephalosporin\(^1\) or fluoroquinolone for at least 72 hours within 7 days?

  - **Does the patient have a beta-lactam allergy?**
    - **NO**
      - **Cefepime 1 gm (60-90”)**
      - **Amikacin 15mg/kg (30”)**
      - **Vancomycin 1-1.5 gm (60-90”)**
    - **YES**
      - **Amikacin 15mg/kg (30”)**
      - **Levofloxacin 750 mg (60-90”)**
      - **Vancomycin 1-1.5 gm (60-90”)**

  - **NO**
    - **Does the patient have a fluoroquinolone allergy?**
      - **YES**
        - **Aztreonam 2 gm (15”)**
        - **Amikacin 15mg/kg (30”)**
        - **Vancomycin 1-1.5 gm (60-90”)**
      - **NO**
        - **Meropenem 1 gm (15”)**
        - **Amikacin 15mg/kg (30”)**
        - **Vancomycin 1-1.5 gm (60-90”)**

- **Intra-abdominal catastrophe suspected?**
  - **NO**
    - No additional antibiotics
  - **YES**
    - **ADD**
      - **Metronidazole 500mg (30”)**
      - **Caspofungin 70 mg (60”)**

1\(^{rd}\) or 4\(^th\) gen cephalosporins = cefepime, ceftazidime.

2Vancomycin dose: weight ≤ 70kg = 1 gm x 1, weight > 70kg = 1.5gm x 1

3Infuse vancomycin before caspofungin (if given), but after other antibiotics have

Approved by N Fishman, Infectious Disease 10/2007
Approved for use by RRT Babak Sarani, Bill Schweikert
Treatment - Steroids

- Recommended only for shock refractory to pressors
- Annane – multicenter, European, RCT
  - Pts with vasopressor-resistant hypotension
  - Improved mortality if rise in cortisol following ACTH was < 9mcg/dL and if baseline cortisol < 21
- CORTICUS – larger, European, RCT
  - All pts with septic shock (regardless of vasopressor response)
  - No difference in mortality but vasopressor sparing effect with steroids
  - ACTH stim could not predict who was steroid deficient

Annan 2002; 288:862

Insert CORTICUS Reference
Treatment - Xigris

• Activated protein C
  – Anticoagulant (inhibits Factors V and VIII)
    • Stop microthrombi formation and prevent end-organ loss?
  – Endothelial cell stabilizer (anti-inflammatory)
    • Stop excessive production of cytokines and apoptosis?
Treatment - Xigris

• PROWESS – RCT, 1690 pts, stopped early
  – 532 surgical pts
  – 6% decrease in mortality overall
    • Greatest decrease if APACHE II score > 25
    • Greater decrease in medical pts
      – Surgical pts 3% decrease mortality overall and 9% decrease if abdominal operation performed (better source control)
  – 1.5% increase in risk of bleeding
    • Equal between medical and surgical groups
PROWESS - Limitations

- Never replicated
- Entry criteria changed in the middle of the study
- Study terminated early
- Drug approved for use in a post-hoc derived subgroup (APACHE II > 25 or high risk of death as determined by intensivist)
- Higher APACHE II mortality in the control arm than anticipated