What is Sepsis?

- **Systemic Inflammatory Response Syndrome (SIRS):**
  - Temp >38°C or <36°C
  - Heart Rate > 90 bpm
  - Resp Rate > 20/min
  - WBC >10000, <4000, or Bandemia >10%

- **Sepsis:** SIRS + Infection
- **Severe Sepsis:** Sepsis + Organ Dysfunction
- **Septic Shock:** Sepsis + Refractory Hypotension

- **Sepsis:** presence of sepsis, plus organ hypoperfusion or dysfunction
- **Organ Hypoperfusion:**
  - Reduced organ perfusion, e.g., decreased organ function or tissue hypoxia
  - Low cardiac output
  - Low blood pressure

- **Septic Shock:**
  - Presence of sepsis
  - Refractory hypotension:
    - Systolic blood pressure < 90 mm Hg
    - Mean arterial pressure < 65 mm Hg or < 60 mm Hg drop in systolic blood pressure compared to baseline
    - Unresponsive to a fluid challenge of 20–40 mL/kg
    - Vasopressor dependency after adequate volume resuscitation

Organ Dysfunction +/- Hypotension

Severe Sepsis – presence of sepsis, plus organ hypoperfusion or dysfunction

- **Organ Dysfunction:**
  - Failure of one or more organ systems
  - Reduced organ perfusion, e.g., decreased organ function or tissue hypoxia
  - Low cardiac output
  - Low blood pressure

- **Septic Shock:**
  - Presence of sepsis
  - Refractory hypotension:
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Infection

Toxin, Molecular Signaling Paths

- Vasodilatation
- Myocardial Depression
- Tissue Microthrombosis
- Neuroendocrine Effects

*Initially, later anti-inflammatory host response

Conflict of Interest

- No Conflicts
Sepsis: Source Control

- **EARLY, BROAD, EMPIRIC antibiotic therapy**
- Not the time to be elegant!
- Think of sources needing **SURGICAL INTERVENTION**
  - Catheter/device → Remove it
  - Soft tissue abscess → Drain it
  - Empyema → Chest tube
  - Cholangitis → ERCP
  - Endocarditis → Abx/Valve replacement
  - Septic arthritis → Joint debridement
- Narrow therapy after 48 – 72H of cultures

Septic Shock: **EARLY Goal-Directed Therapy**

*Treatment began in E.D.: 6-hours
*A-line, Central line insertion
*Monitored: Mean arterial BP (MAP)
  - Central venous pressure (CVP)
  - Central venous O2 sat (ScvO2)
  - Hematocrit

---

**Oxygen Supply vs. Demand**

- Central venous oxygen content (SvO2)
- Venous oxygen content (SO2)
- Oxygen extraction
- Oxygen delivery

**EARLY Goal-Directed Therapy**

**HOW'D THEY DO THAT??**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hours after the Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 h</td>
<td>7-12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total fluids (ml)</th>
<th>899 ± 2438</th>
<th>90,602 ± 216</th>
<th>13,358 ± 7,725</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard therapy</td>
<td>4981 ± 2994</td>
<td>8,625 ± 5,162</td>
<td>12,443 ± 5,396</td>
</tr>
<tr>
<td>EGDT</td>
<td>5.0 ± 0.1</td>
<td>6.8 ± 0.3</td>
<td>7.3 ± 0.4</td>
</tr>
<tr>
<td>Red cell transfusion (%)</td>
<td>18.5</td>
<td>32.5</td>
<td>44.5</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>18.5</td>
<td>32.5</td>
<td>44.5</td>
</tr>
<tr>
<td>EGDT</td>
<td>64.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any vasopressor (%)</td>
<td>30.3</td>
<td>42.9</td>
<td>51.3</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>30.3</td>
<td>42.9</td>
<td>51.3</td>
</tr>
<tr>
<td>EGDT</td>
<td>27.4</td>
<td>29.1</td>
<td>36.8</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.62</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Any vasopressor (%)</td>
<td>30.3</td>
<td>42.9</td>
<td>51.3</td>
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**Early Goal-Directed Therapy**

**IT WORKED!!**

**2010: What are the key components and broader applicability of EGDT?**
“Fill the Tank”

\[ \text{DO}_2 = \text{C.O.} \times \text{CaO}_2 \]
\[ \frac{\text{SV}}{\text{HR}} \]
\[ \frac{\text{LVEDV}}{\text{contractility}} \]

* \( \text{CaO}_2 = 1.34 \times \text{Hgb} \times \text{SaO}_2 \)

Volume resuscitation

- Must restore intravascular volume
- Need rapid & aggressive use of crystalloid or appropriate colloid
- Deliver as bolus infusion (via 2 large-bore iv’s and/or Cordis)
- Avoid use of vasopressors as will potentially exacerbate tissue hypoxia
- Treat the underlying problem


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**Action of Vasoactive Catecholamines**

<table>
<thead>
<tr>
<th>Catecholamine</th>
<th>( \beta_1 )</th>
<th>( \beta_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>HR, Contractility</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chest 2007; 132:1678-1687

**SAFE Study, NEJM 2004; 350:2247.**

Primary endpoint: 28d Mortality

No Significant Difference

(\( \text{DA}: 52.5\%, \text{NE}: 48.5\% \))

**Vasopressin as a ‘Pressor’?**

- \( ? \) Vasopressin deficiency in sepsis
- Multi-center RCT with ~800 patients
- No significant mortality benefit in adding vasopressin to norepinephrine
- Less sick people did better with addition of vasopressin

“Official” Role of Vasopressin?

- "No randomized, controlled data are available to determine the best agent to treat patients with septic shock that is unresponsive to norepinephrine, but my experience and several observational studies suggest that vasopressin will restore adequate blood pressure in a substantial number of such patients."

(2008 NEJM Editorial)

Other “goals” of therapy That can be monitored?

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy
A Randomized Clinical Trial

Conclusions: Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize ScvO2 did not result in significantly different in hospital mortality.

Trial Registration: clinicaltrials.gov identifier: NCT00372502

Can We Fix the Microcirculation?

Activated Protein C (rhAPC) in Sepsis: 2001

Lilly Announces Withdrawal of Kigrisa Following Recent Clinical Trial Results

INDIANAPOLIS, October 26, 2011 (PRNewswire) --

Eli Lilly and Company announces withdrawal of its intravenous (intravenous infusions) product in all markets following results reported today from a large, randomized, double-blind, placebo-controlled clinical trial conducted in non-United States patients who had severe sepsis or septic shock. The trial was designed to support the regulatory approval of Kigrisa (pentosan polysulfate sodium) intravenous infusions given in addition to standard-of-care therapies. The trial evaluated the efficacy of Kigrisa as a mitochondrial activator in terms of decreasing lactate levels and improving survival in patients with severe sepsis or septic shock. The study findings, however, did not meet the primary endpoint of improving survival in patients treated with Kigrisa compared to placebo.

Lilly and Company are in the process of notifying health care professionals and clinics involved in patient care. In addition, the study findings were presented at the recent 2011 World Congress of the International Conference on the Systemic Inflammatory Response Syndrome (SIRS) in Berlin, Germany.

"While there were no new safety findings, the study failed to demonstrate that Kigrisa improved patient survival and thus does not support the extension of its use in this indication," said W. Darrin Gamez, M.D., Lilly's Senior Vice President of Development for Infections. "Given the promising mitochondrial activator concept, we are continuing to explore the clinical potential of Kigrisa in other settings." "Kigrisa is an example of Lilly's commitment to new therapies that hold the promise of responding to unmet medical needs. We look forward to continuing to work with our partners in developing a new agent that improves the survival of patients with severe sepsis and septic shock, while also exploring new means of addressing the unmet needs of patients with SIRS in the future,"said Gamez.

"The safety profile of Kigrisa has not been altered by these results and we believe that it remains an important treatment for patients with severe sepsis or septic shock," said Gamez. "We believe that the concept of using an agent that stimulates mitochondrial function to improve patient outcomes is still valid and that more studies need to be conducted to determine the potential of this approach in both severe sepsis and septic shock." "It is worth noting that the original approval for Kigrisa was based on a single study and these recent results were quite unexpected," Gamez noted. "A continuing factor to these study results must be added in the standard of care for treating severe sepsis over the next 10 years."

Up for a good debate?

Point: Adherence to Early Goal-Directed Therapy: Does It Really Matter? Yes. After a Decade, the Scientific Proof Speaks for Itself

Counterpoint: Adherence to Early Goal-Directed Therapy: Does It Really Matter? No. Both Risks and Benefits Require Further Study

Gregory A. Schmidt

Chest 2011; 139; 496-503

DOI 10.1378/chest.10-1405
RELATIVE Adrenal Insufficiency

Basic Background

- “High-dose” corticosteroids DO NOT improve sepsis outcomes

- Absolute adrenal insufficiency in sepsis is RARE

- What about RELATIVE adrenal insufficiency?

Relative Adrenal Insufficiency, 2002


c8 Relative Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Patients with Relative Adrenal Insufficiency</th>
<th>Patients without Relative Adrenal Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ STEROIDS</td>
<td>- STEROIDS</td>
</tr>
</tbody>
</table>

Relative Adrenal Insufficiency, 2002

The ACTH-Stim Test Story

Annane et al. *JAMA* 2002 288: 862

- 300 septic patients
  - 149 Patients: Placebo
  - 151 Patients: Hydrocortisone 50 mg IV Q6h + Florinef 50 μg PO QD x 7 days

- All got:
  - Baseline, random cortisol levels
  - 250 μg ACTH stimulation test
  - "Nonresponder": Increase cortisol < 10 μg/dL
  - "Responder": Increase cortisol ≥ 9 μg/dL
Adjunctive Sepsis Care

- Relative Adrenal Insufficiency
  - "Old protocol": Treat if random cortisol <15 or increase of <10 with ACTH-stim?
  - "New approach": Perhaps consider low-dose steroids only for sickest patients not responsive to vasopressors?
- Glucose Control
  - Target glucose liberalized to <150 mg/dL.

Take-Home Points: Sepsis-I

- Early Identification of Patients with Sepsis
- Source Control and Early Broad-Spectrum Antibiotics
- Early Goal Directed Therapy
- Levophed and Dopamine First Pressors of Choice
- Consider Addition of Vasopressin to Levophed
- Consider Epinephrine as 2nd-line Agent for Refractory Hypotension to Levophed or Dopa

Take-Home Messages-II

- NO MORE ACTIVATED PROTEIN C
- Consider low-dose hydrocortisone for patients with sepsis-induced refractory hypotension despite fluids and pressors (and ACTH stim test likely isn’t helpful).
- Uncertain goal of glucose control, but target <150 mg/dL (instead of tighter control) suggested until more data available. Hourly monitoring of glucose levels while on an insulin drip is critical, and avoid hypoglycemia.
- Attention to standard ICU care (e.g., ventilator bundle, DVT and GI prophylaxis, central line care, etc.).
**Question #1**

A 47 yo woman with alcoholic cirrhosis is brought to your ER with fevers, confusion, shortness of breath, and worsening ascites. SBP is 50 mmHg, HR 150 bpm, RR 40/min, and O₂ sat 80%. CXR shows diffuse infiltrates, and peritoneal fluid returns with a leukocyte count of 1000/μL (95% polys). Initial management of hemodynamics should entail use of:

a. Vasopressin  
b. Norepinephrine  
c. Norepinephrine + Lasix  
d. Central line insertion  
e. Dobutamine

*Treatment began in E.D.: 6-hours  
*A-line, Central line insertion  
*Monitored: Mean arterial BP (MAP)  
Central venous pressure (CVP)  
Central venous O₂ sat (S_CVO₂)  
Hematocrit

**Question #2**

Your administer broad-spectrum antibiotics to treat presumed spontaneous bacterial peritonitis, give her supplemental O₂ (now saturating 90% on 100% FM), and after fluid resuscitation with 3L of crystalloid, her HR comes down to 100 bpm, her SBP has risen to 65 mm Hg with a mean arterial pressure (MAP) of 50 mm Hg, and the CVP is 13 mm Hg. You next order:

a. Vasopressin  
b. Norepinephrine  
c. Norepinephrine + Lasix  
d. 1 Unit of PRBCs  
e. Dobutamine
**Question #3**

A 47 yo woman with multilobar pneumonia is admitted to your ICU. She is intubated and aggressively fluid-resuscitated. Despite support with EGDT, including fluids and norepinephrine, her BP remains 60/40 mmHg with development of renal failure and mottled extremities. Which of the following adjunctive therapies are not plausible?

a. Vasopressin  
b. Low dose hydrocortisone (25 mg i.v. q6h)  
c. Activated Protein C  
d. Low tidal volume ventilation

**Question #4**

A 47 yo woman with multilobar pneumonia is admitted to your ICU. Broad spectrum antibiotics are given, and she is intubated and aggressively fluid-resuscitated. She is supported with EGDT, vasopressors, and with refractory hypotension, you add low-dose hydrocortisone to her regimen. Her bedside fingerstick glucose returns at 275 mg/dL. You next order:

a. No specific treatment—continue monitoring and treat only if glucose rises above 300 mg/dL  
b. A D10 drip  
c. Continuous insulin infusion, target glucose<150 mg/dL