New Frontiers in Sepsis Resuscitation

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Conflicts of Interest
None

Topics to Cover
• How we think about sepsis
• Early recognition
• Early treatment
  • Antibiotics, fluids, pressors
• Emerging therapies
Greeks believed that tissue decomposed in two ways:

- **Pepsis** = “life-giving” = fermentation
- **Sepsis** = death/decay = putrefaction

**SIRS**

Systemic Inflammatory Response Syndrome

Two of following:
- Temp >38°C or <36°C
- HR >90
- RR >20 or PaCO2 <32 mmHg
- WBC >12 or <4 or bands >10%

Infection - Sepsis - SIRS

- Bacteremia
- Fungemia
- Parasitemia
- Viremia
- Other
- Trauma
- Burns
- Pancreatitis
Sepsis

Sepsis = SIRS due to infection
Severe sepsis = sepsis with end-organ dysfunction
Septic shock = severe sepsis w/ HoTN refractory to fluids


R. Phillip Dellinger, MD, Mitchell L. Levy, MD, Andrew Rhodes, MB, BS, FACP, Intensivist, MD, Stephen J. Sibbald, MD, Charles L. Sprung, MD, Joan L. Angus, MD, Bruce W. Cerra, MD, Mark E. Nunnally, MD, Scott E. Tompkins, MD, Robert F. Vincent, MD, PhD, John A. Morris, MD, PhD, and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup

Table 1: Diagnostic Criteria for Sepsis

<table>
<thead>
<tr>
<th>Diagnosis of Sepsis</th>
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<tbody>
<tr>
<td>Fever (38°C)</td>
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<tr>
<td>Hypothermia (rectal temperature &lt; 36°C)</td>
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<tr>
<td>Rapid heart rate (&gt;100/min)</td>
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<td>Respiratory rate (&gt;20/min)</td>
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<td>Hypotension (BP &lt; 90 mm Hg systolic)</td>
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<td>Lactic acidosis (lactate &gt; 4 mmol/L)</td>
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<td>New or worsening organ dysfunction</td>
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Continuous positive airway pressure (CPAP) |

Acute organ dysfunction defined by a reduction in organ function or failure that meets one of the following criteria: 

- Respiratory (ARDS) 
- Gastrointestinal (reduced urine output < 0.5 mL/kg/h or serum creatinine > 1.5 mg/dL) 
- Cardiovascular (systolic blood pressure < 90 mm Hg) 
- Neurologic (Glasgow Coma Scale < 8) 
- Hepatic (intrahepatic or extrahepatic 

Hypoproteinemia (serum albumin < 2.5 g/dL) 

Severe sepsis and septic shock were defined using the Surviving Sepsis Campaign Guidelines, as follows: 

- Severe sepsis: The presence of SIRS with evidence of infection and organ dysfunction 
- Septic shock: Severe sepsis with hypotension refractory to fluids
Surviving Sepsis

A. Initial Resuscitation
B. Screening for Sepsis & Performance Improvement
C. Diagnosis
D. Anti-microbial therapy
E. Source Control
F. Infection Prevention

**Table 1: Recommendations: Initial Resuscitation and Infection Issues**

**A. Initial Resuscitation**
1. Protocolised, goal-directed resuscitation of patients with sepsis-related tissue hypoperfusion (defined as in the document on hypoperfusion persisting after initial fluid challenge or fixed lactate concentration ≥5 mmol/L despite the fluid resuscitation). 
2. Central venous pressure <6 mmHg.
3. Urine output <0.5 mL/kg/h.
4. Central venous oxygen saturation <70% or 65%, respectively (grade 1C).
5. In patients with elevated lactate levels targeting resuscitation to normal lactate (grade B).

**B. Screening for Sepsis and Performance Improvement**
1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital-based performance improvement efforts in severe sepsis (grade 1C).

**C. Diagnoses**
1. Cultures as clinically appropriate before antimicrobial therapy if significant delay (>45 min) in the start of antimicrobial therapy (grade 2C). If initiated within 2 h after diagnosis (both septic and non-septic) or (b) in the absence of antimicrobial therapy with at least 6 h before punctures and 1 h before insertion of vascular access devices, unless the device was recently (within 24 h) inserted (grade 1C).
2. Use of 1.0-3 g/kg/digoxin therapy (grade 2B), vancomycin and ampicillin therapy except S. aureus; if available and necessary, antimicrobials are in a differential diagnosis of source of infection (grade 1C).
3. Imaging studies performed promptly to confirm a potential source of infection (grade 1C).

**D. Antimicrobial Therapy**
1. Administration of effective intravenous antimicrobial therapy within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 2B) as the goal of therapy.
Antibiotics

**1967 Brit J Clin Practice.** *An investigation to evaluate a top ABX in the prevention of wound sepsis in a casualty department.*

- Decreased mortality from sepsis, syphilis, meningitis
- No change from scarlet fever, erysipelas, ARF, PNA, bronchitis, TB, typhoid, AGE, meningococcus

**1979 Review of Infectious Diseases**
- Human stool into rat peritoneum +/- antibiotics
- Clinda/tobra > ceph/tobra, clinda/tobra, cefamandole

**1977 Lancet.** *Prophylactic systemic ABX in colorectal surgery.*
- 48% mortality in controls vs 4% with gent/flagyl

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**Antibiotics**

**1995 Pediatric Infectious Disease**
- Pediatric pneumonia – Augmentin = cefpodoxime

**1995 American J Emergency Medicine**
- No advantage to empiric ABX for wounds (n=1734)

**1997 Antimicrobial Agents & Chemotherapy**
- CAP (n=456) Levofoxacin PO = Ceftriax 1M/IV

**1998 Archives of Internal Medicine**
- Pyelo/urosepsis (n=66) cip ro PO = cipro IV

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**Graph:**

Odds of Death

<table>
<thead>
<tr>
<th>Time to ABX (hrs)</th>
<th>0.1</th>
<th>1.3</th>
<th>3.6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds of Death</td>
<td>0</td>
<td>0.2</td>
<td>0.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Kumar (2006) *Crit Care Med*

Kumar (2009) *Chest*
Kumar (2009) *Chest*

### Fluid Therapy in Severe Sepsis

1. Crystalline as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients may require substantial amounts of albumin (grade 1B).
4. Initial fluid challenge is patients with vaso-occluded tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 cc/kg of crystalloid is a portion of this may be albumin equivalent. More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique to be applied wherein fluid administration is continued as long as there is hemodynamic improvement after fluid administration (10 L crystalloid in 2 hours), without vascular volume expansion or clinical signs of hypovolemia (grade 1B).

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**Recent Advances in Chest Medicine**

**Fluid Therapy in Resuscitated Sepsis**

*Less Is More*

Lubovin Davydov, MD, and Gregory A. Schwab, MD, FCCP

Fluid infusion may be beneficial in patients with severe sepsis, especially in the earliest phases of treatment. Following initial resuscitation, however, fluid boluses often fail to augment perfusion and may be harmful. In this issue, we review the components and regulation of fluid intake to early fluid resuscitation in sepsis, and discuss the potential benefits and risks of fluid resuscitation in sepsis. The role of fluid resuscitation in sepsis is complex, and the optimal fluid therapy for severe sepsis is not well established. The authors review the current evidence regarding the optimal fluid therapy for severe sepsis, and recommend a clinical approach.
N. Vasopressors

1. Vasopressor therapy initially targets a mean arterial pressure (MAP) of 70 mm Hg (grade 1C).

2. IPPV should be the first choice vasopressor (grade 99).

3. Vasopressin is labeled b and potentially diluted for non-neutrophils when an additional agent is needed to maintain adequate blood pressure (grade 2B).

4. Vasopressin (10 U/h) or norepinephrine (0.5 mcg/kg/min) should be started or increased (grade 2D).

5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressor doses higher than 10 U/h or norepinephrine should be considered for salvage therapy (grade 2D).

6. Dopamine is an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of sepsis-induced shock, and adequate urine output and grade 2D).

7. Norepinephrine is not recommended for the treatment of septic shock except in circumstances where other vasopressors are associated with worsening and impaired blood pressure persistently low (less than 70 mm Hg) for more than 24 hours (grade 1A).

8. Low-dose dopamine should not be used for renal protection (grade 1A).

9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (grade 1D).

I. Interventions: Therapy

A. A target of absolute oxygen saturation up to 96% micrograms/kg/min be administered or added to vasopressor (V1) in the presence of bid reversible dysfunction as suggested by elevated cardiac filling pressure and low or ille factor output, or (2) ongoing signs of hypotension, elevated intracranial volume, and decreased MAP (grade 1C).

B. No single strategy to increase cardiac index to be determined in a sequential order (grade 1B).

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**Surviving Sepsis Campaign Bundles**

**TO BE COMPLETED WITHIN 1 HOURS:**
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad-spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

**TO BE COMPLETED WITHIN 6 HOURS:**
5) Apply vasopressor (MAP hypertension that does not respond to initial fluid resuscitation)
6) In the event of persistent arterial hypertension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L, ≥40 ng/mL:
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo2)*
7) Remasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo2 of ≥70%, and normalization of lactate.
Steroids?

1987 NEJM 223 septic pts RDBPC
• No mortality benefit (steroids 21% - controls 22%)
• No benefit in sepsis (19% - 21%)
• No benefit w/Gm- (17% - 25%, 7% - 27% blood cx)
• Slower resolution of secondary infections

1987 NEJM 382 septic patients RDBPC
• Mortality increased with steroids 59% vs. 29%

Steroids?

1999 Academic Emergency Medicine
• 57 hypotensive non-trauma patients
• 14% with baseline cortisol <20ug/dl
• Another 5% with abnormal ACTH-stim test

1994 Clinical Investigator
• 57 patients with sepsis or septic shock
• Low-dose hydrocortisone infusion
• Decreased SIRS, decreased shock, decreased inflammatory mediators
Sepsis at UCSD

- Diagnose “far forward”
- Tiered approach
- Risk factors
  - Any HoTN significant
  - Tachycardia important
  - Bandemia, hyperlactemia
  - Serial values
  - Watch GI bleeds

Sepsis at UCSD

- Immediate antibiotics
- Keep your “foot on the gas”
- Think about steroids
- Watch post-RSI crash
- Other stuff
  - ICU “bounces” and diuretics
  - Diurnal variability
Trauma
Sepsis
Macrophages
PLA2
TNF, chemokines
IL-1
PAF, eicosanoids
PMN, endothelium
Tissue Damage

Sepsis
Trauma
Macrophages
PLA2
TNF, chemokines
IL-1
PAF, eicosanoids
PMN, endothelium
Tissue Damage

ACTIVATION
LPS
LPS-Binding Protein (LBP)
CD 14
Cellular signaling
**Anti-LPS-Ab**

1982 NEJM 212 septic patients RDBPC
- Mortality in controls (39%) > treatment group (22%).
- With profound shock - 77% versus 44%

1991 NEJM 543 septic pts RDBPC
- With GNR cx (n=200) - controls 52% > treatment 37%
- Overall, no difference - controls 43% = treatment 39%

1991 JAMA 486 septic patients RDBPC
- No difference overall and in all pts with GNR cx.
- With GNR cx and no shock (n=137), RR=2.3 survival.

1997 Critical Care 2199 septic pts RDBPC
- No overall difference.

**LPS-Neutralizers**

1993 J Infectious Disease Mouse model
- Mortality in controls (87%) > treatment group (7%).
- Coincident administration, continuous infusion.

1992 J Infectious Disease Rabbit model
- Induced menincococcemia = control mortality 92%
- Pretreated - 48%
- Co-administered - 10%
- 30 min delay - 67%

**Summary**

Aggressive diagnosis
- Tiered approach

Aggressive treatment
- Antibiotics, fluids
- Pressors

Frequent reassessment
- Diagnosis/disposition
- Response to therapy