The Management of Septic Shock

Anthony J. Courey, MD
Assistant Professor of Medicine
Associate Director, CCMU
Pulmonary & Critical Care Medicine
Conflicts & Disclosures

- No conflicts
- No disclosures
Overview and Objectives

- Definitions and clinical criteria for diagnosis
- Epidemiology
- Recognition
- Early Goal Directed Therapy
- Recent sepsis resuscitation trials
- Surviving Sepsis Guidelines
Overview of Surviving Sepsis Guidelines

• Initial Resuscitation
• Fluid Therapy
• Vasopressor Therapy
• Inotropic Therapy
• Antibiotics & Other Therapies
• Source Control
Definitions & Clinical Criteria
Definitions of Sepsis

- A clinical **syndrome** – not a specific disease with a single specific cause
  - e.g. Flu-like syndrome vs actual influenza virus infection
  - We use syndromes to more easily recognize and prevent morbidity and mortality with common illness, e.g. asthma, hypertension, “flu” and sepsis

- **Infection-induced systemic inflammatory response**

- Recognition of sepsis syndrome severity is also important

Bone RC et al, Chest 1992;101:1644
Systemic Inflammatory Response Syndrome (SIRS) Criteria

- **Temperature** > 38 C or < 36 C
- **Heart rate** > 90
- **Respiratory rate** > 20
- **PaCO2** < 32 mm Hg
- **WBC** > 12 or < 4
- > 10% Bands/Immature Segs
- “**THeRe aRe CO2WBoyS**” mnemonic
### Definitions of Sepsis Severity

#### Possible Sepsis
- Two or more of the following:
  - Body temperature > 38.5°C or < 35.0°C
  - Heart rate > 90 beats per minute
  - Respiratory rate > 20 breaths per minute or arterial CO₂ tension < 32 mm Hg or need for mechanical ventilation
  - White blood cell count > 12,000/mm³ or < 4,000/mm³ or immature forms > 10%

#### Confirmed Sepsis
- Systemic inflammatory response syndrome and documented infection (culture or gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection—eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)

#### Severe Sepsis
- Sepsis and at least one sign of organ hypoperfusion or organ dysfunction:
  - Areas of mottled skin
  - Capillary refill time ≥ 3 s
  - Urinary output < 0.5 ml/kg for at least 1 h or renal replacement therapy
  - Lactates > 2 mmol/L
  - Abnormal change in mental status or abnormal electroencephalogram
  - Platelet counts < 100,000/mL or disseminated intravascular coagulation
  - Acute lung injury—acute respiratory distress syndrome
  - Cardiac dysfunction (echocardiography)

#### Septic Shock
- Severe sepsis and one of:
  - Systemic mean blood pressure < 60 mm Hg < 80 mm Hg if previous hypertension) after 20–30 mL/kg of 0.9% saline or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg
  - Need for dopamine > 5 μg/kg per min or norepinephrine or epinephrine < 0.25 μg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

#### Refractory Septic Shock
- Need for dopamine > 35 μg/kg per min or norepinephrine or epinephrine < 0.25 μg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

---

*Annane et al, Lancet 2005;365:63*
Sepsis = SIRS + Infection

Bone RC et al, Chest 1992;101:1644
SIRS vs Sepsis Severity-Mortality

Sepsis severity is more than just numbers!

Martin et al, NEJM 2003; 348: 1546-1554
NEJM 2015:

ANZICS group:
You don’t have to meet 2 SIRS criteria to die of sepsis!

Figure 1. Mortality among Patients with Severe Sepsis, According to Status with Respect to Criteria for the Systemic Inflammatory Response Syndrome

Kaukonen et al, NEJM 2015; 327: 1629-1638
Epidemiology
**Epidemiology of Sepsis-Incidence**

It’s Not Just the Years, but the Miles

- **Age**
- **Male sex**
- **African American**
- **Acute organ failure**
  - Renal
  - Cardiovascular
  - Neurological
  - Respiratory
- **Co-morbidities**
  - Diabetes
  - Malignancy
  - Alcoholism
  - HIV infection
  - Immunosuppression
- **Chronic organ failure**
  - CHF
  - Chronic liver disease

Martin et al, NEJM 2003; 348: 1546-1554
Recognition

...Always begins with the ABCs
...And a high index of suspicion
... Sepsis-Induced Organ Dysfunction
Always start at the beginning

• **A: Airway:** Independent life is impossible without it

• **B: Breathing:** 53% of both arms of the Early Goal-Directed Therapy landmark RCT were intubated within 6 hours

• **Circulation:** Assess organ perfusion & IV access:
  - BP, skin, mental status, elevated lactate levels (>2 mmol/L)
In 3,518 patients matched on the propensity for treatment, receipt of a neuromuscular blocking agent was associated with a reduced risk of in-hospital mortality (risk ratio, 0.88; 95% CI, 0.80, 0.96).
Sepsis Induced Organ Dysfunction

- Vascular: Relative IVVD $\rightarrow$ Hypotension
- Cardiac: Sepsis cardiomyopathy
- Pulmonary: Noncardiogenic pulmonary edema $\rightarrow$ ARDS
- Renal: Intravascular volume depletion $\rightarrow$ Hypoperfusion $\rightarrow$ Acute Kidney Injury (AKI) $\rightarrow$ Acute tubular necrosis (ATN)
- GI: Stress ulceration, hypoalbuminemia, gut bacterial translocation
Sepsis Induced Organ Dysfunction

- Blood: Decreased RBC deformability → Hemolysis and microthrombi → Impaired microcirculation → Global tissue hypoxia

- Platelets: Nonspecific tissue activation → Microthrombi; platelet consumption → DIC with bleeding and clotting risks

- Leukocyte & Compliment: Activation → Indiscriminate organ injury

- Brain: Encephalopathy, confusion, agitation are NOT benign (e.g. CURB-65 mortality indicator in pneumonia)
Skin:

- **EARLY**: Vasodilated, high cardiac output → WARM

- **LATE**: Intravascular hypovolemia, poor cardiac output, shunting to vital organs, microthrombi → COLD
  - Mottling
  - Petechiae and purpura with DIC
Skin Mottling Predicts Sepsis Mortality
Disseminated Intravascular Coagulation (DIC)

In meningococcemia called purpura fulminans
Early Goal-Directed Therapy

… A revolution in the care of septic shock
Early Goal-Directed Therapy

- Randomized, prospective, single center trial treatment
- 260 patients randomized
- 2/4 SIRS criteria and SBP < 90 mmHg or lactate > 4 mmol/L
- Patients randomized to 6 hours of goal-directed therapy vs standard therapy

Rivers et al, NEJM 2001
Prior to EGDT all pts received a 20-30 cc/kg bolus of 0.9% saline.

IF good findings move down; IF bad turn right!
**EGDT: Results**

**Table 3. Kaplan-Meier Estimates of Mortality and Causes of In-Hospital Death.***

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERAPY (N = 133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N = 130)</th>
<th>RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>59 (46.6)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**ARR Death = 46.5 – 30.5 = 16%**

**NNT = 7**
### EGDT: Results

#### Treatment Group Differences in the first 6 hrs:

1. More IVF
2. More PRBC
3. More ionotrope

#### Table 4. Treatments Administered.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hours after the Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–6</td>
</tr>
<tr>
<td>Total fluids (ml)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3499±2438</td>
</tr>
<tr>
<td>EGDT</td>
<td>4981±2984</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red-cell transfusion (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>18.5</td>
</tr>
<tr>
<td>EGDT</td>
<td>64.1</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any vasopressor (%)†</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>30.3</td>
</tr>
<tr>
<td>EGDT</td>
<td>27.4</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inotropic agent (dobutamine) (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>0.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>13.7</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>53.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>53.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
</tr>
<tr>
<td>Pulmonary-artery catheterization (%)‡‡</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3.4</td>
</tr>
<tr>
<td>EGDT</td>
<td>0.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
</tr>
</tbody>
</table>

At 72 hrs the total IVF difference between groups is <100 cc.


Surviving Sepsis Guidelines for the Management of Severe Sepsis & Septic Shock

... And some of the supporting evidence

Formed in 2002

Updated Bundles in Response to New Evidence
Recommendation #1: Initial Resuscitation

- We recommend the protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or lactate $\geq 4$ mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission.

- We suggest, in patients with elevated lactate levels as a marker of tissue hypoperfusion, targeting resuscitation to normalize lactate as rapidly as possible. (Grade 2C)
Recommendation #1: Initial Resuscitation GOALS

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

* "Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.
The Surviving Sepsis Guidelines

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER
  • Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:
  • Measure CVP
  • Measure ScvO₂
  • Bedside cardiovascular ultrasound
  • Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Of note, the 6-hour bundle has been updated; the 3-hour SSC bundle is not affected.
The Evidence: Lactate Clearance

Mortality (%)

Jones A. JAMA. 2010;303:739–746
348 patients: decrease in lactate levels of 20% or more in the first 8 hours, in addition to ScvO₂ target achievement, and was associated with a 9.6% absolute reduction in mortality.

Recommendation #2: Fluid Therapy

- We recommend **crystalloids** be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock. *(Grade 1B)*
- We recommend **against the use of hydroxy-ethyl starches** for fluid resuscitation of severe sepsis and septic shock. *(Grade 1B)*
- We recommend an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a **minimum of 30 mL/kg of crystalloids** (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients. *(Grade 1C)*
Recommendation #2: Fluid Therapy

• We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (Ungraded).

• My favorite quote “A fluid bolus is a liter or more in thirty minutes or less… and more may need to be given”
  • R. Phillip Dellinger, Surviving Sepsis Guidelines
The Evidence: Albumin vs. Crystalloid

ALBIOS Study

The Evidence: Albumin vs. Crystalloid

Albumin recommended in severe sepsis and septic shock when significant crystalloid has been given

Christian J. Wiedermann, et al, Meta-analysis of pooled data from the three large trials.
Recommendation #3: Vasopressors

- We recommend that vasopressor therapy initially target a mean arterial pressure (MAP) of 65 mm Hg. (Grade 1C)

- We recommend norepinephrine as the first-choice vasopressor. (Grade 1B)

- We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure. (Grade 2B)
**Recommendation #3: Vasopressors**

- **Vasopressin up to 0.03 units/minute can be added to norepinephrine** with the intent of raising MAP to target or decreasing norepinephrine dosage.

- **Low-dose vasopressin is not recommended as the single initial vasopressor** for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).

- **We suggest dopamine** as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of arrhythmias and/or low heart rate). *(Grade 2C)*
The Evidence: NE vs Dopamine
Meta-Analysis

Information from 4 randomized trials (n=540) comparing norepinephrine to epinephrine found no evidence for differences in the risk of dying (RR=0.96; 0.77 to 1.21; fixed effect; I²=0%).

Meta-analysis performed by Djillali Annane for Surviving Sepsis Campaign, using following publications:

Information from 4 randomized trials (n=540) comparing norepinephrine to epinephrine found no evidence for differences in the risk of dying (RR=0.96; 0.77 to 1.21; fixed effect; $I^2=0\%$).

Recommendation #5: Ionotropes

- We recommend that a trial of dobutamine infusion up to 20 \( \mu g/kg/min \) be administered or added to vasopressor (if in use) in the presence of: (Down-graded in response to PROCESS, ARISE and PROMISE trials)
  - **myocardial dysfunction** as suggested by elevated cardiac filling pressures and low cardiac output, or
  - ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate mean arterial pressure. *(Grade 1C)*

- We recommend against the use of a strategy to increase cardiac index to predetermined supranormal levels. *(Grade 1B)*
  - *The Schumaker paradigm previously shown to increase mortality!*
Recommendation #6: Diagnostics

We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in the start of antimicrobial(s) administration (Grade 1C).

To optimize identification of causative organisms, we recommend obtaining at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hours) inserted. Blood cultures can be drawn at the same time if from a different anatomic site (Grade 1C).
Recommendation #6: Diagnostics

- Cultures of other sites (preferably quantitative where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection, should also be obtained before antimicrobial therapy if doing so does not cause significant delay in antibiotic administration (Grade 1C).

- We recommend that imaging studies be performed promptly in attempts to confirm a potential source of infection. Potential sources of infection should be sampled as they are identified and in consideration of patient risk for transport and invasive procedures (eg, careful coordination and aggressive monitoring if the decision is made to transport for a CT-guided needle aspiration). Bedside studies, such as ultrasound, may avoid patient transport (Ungraded).
Recommendation #7: Antibiotics

- The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (Grade 1B) and severe sepsis without septic shock (Grade 1C) should be the goal of therapy.

  *Disclaimer:* Although the weight of the evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated.
**Recommendation #7: Antibiotics**

<table>
<thead>
<tr>
<th>Study/yr</th>
<th>Design (no.)</th>
<th>Population /Outcome</th>
<th>Limitation</th>
<th>Other</th>
<th>Outcome Early vs. Late</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar 2006 (1)</td>
<td>Multicenter n=2154</td>
<td>Septic shock only; survival-HD</td>
<td>Retrospective</td>
<td>Time-response relationship</td>
<td>OR for death: 1.119/h delay, P&lt;.0001</td>
<td>Moderate-high for shock</td>
</tr>
<tr>
<td>Berocchie 2010 (2)</td>
<td>Meta-analysis n=654</td>
<td>s/ss/SS; survival 28 days or HD</td>
<td>Observational before-after</td>
<td>n= 4 studies, homogeneous, I²=0%</td>
<td>OR 0.55 (0.33-0.83), P&lt;.0001</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ferrer 2009 (3)</td>
<td>Multicenter (n=2796)</td>
<td>ss/SS; survival-HD</td>
<td>Observational before-after</td>
<td>Time-response relationship</td>
<td>OR 0.67 &lt;1 h, P&lt;.01 OR 0.80 1-3 h, ns OR 0.87 3-6 h, ns</td>
<td>Moderate</td>
</tr>
<tr>
<td>Baric 2005 (4)</td>
<td>Single center n=331</td>
<td>Surgical ICU s/ss; survival-HD</td>
<td>Inception cohort</td>
<td>Time-response relationship</td>
<td>OR 1.1021 [1.003-1.038]/30 min, P&lt;.05</td>
<td>Low</td>
</tr>
<tr>
<td>Levy 2010 (5)</td>
<td>Multicenter (n=15,022)</td>
<td>ss/SS; survival-HD</td>
<td>Observational before-after</td>
<td>&lt;1 h from hospital ward, or &lt;3 h from ED</td>
<td>OR 0.86 (0.79-0.93), P&lt;.0001</td>
<td>Moderate</td>
</tr>
<tr>
<td>El Solh 2008 (6)</td>
<td>Single center (n=174)</td>
<td>Age&gt;65 yr. Septic shock; survival-28 days</td>
<td>Observational matched case-control</td>
<td>&lt;4 h from shock onset; indirect-with other interventions</td>
<td>HR 0.54 (0.33-0.86), P=.01</td>
<td>Low</td>
</tr>
<tr>
<td>Gurnani 2010 (7)</td>
<td>Single center (n=118)</td>
<td>Septic shock; survival-28 days</td>
<td>Observational before-after</td>
<td>&lt;4.5 h from shock onset</td>
<td>OR 0.46 (0.19-0.84), P&lt;.01 by MVR</td>
<td>Low</td>
</tr>
<tr>
<td>Nguyen 2007 (8)</td>
<td>Single center (n=330)</td>
<td>ss/SS; survival-HD</td>
<td>Observational before-after</td>
<td>&lt;4 h from onset</td>
<td>OR 0.38 (0.18-0.80), P&lt;.05 by MVR</td>
<td>Low</td>
</tr>
<tr>
<td>Castellanos-Ortega 2010 (9)</td>
<td>Single center (n=480)</td>
<td>Septic shock; survival-HD</td>
<td>Observational before-after</td>
<td>&lt;1 h from hospital ward, or &lt;3 h from ED</td>
<td>OR 0.68 (0.43-1.09), P=.109 (ns) by MVR</td>
<td>Low</td>
</tr>
<tr>
<td>Gaienski 2010 (10)</td>
<td>Single center (n=261)</td>
<td>ss/SS; survival-HD</td>
<td>Observational cohort study</td>
<td>ED time to effective antibiotic</td>
<td>OR for death 1.135/h delay, P&lt;.05</td>
<td>Low</td>
</tr>
<tr>
<td>Larsen 2011 (11)</td>
<td>Single center (n=345)</td>
<td>Pediatric septic shock-HD</td>
<td>Observational before-after</td>
<td>Pediatric ED time to full bundle, &lt;3 h antibiotic</td>
<td>Mortality reduction 8.4 to 3.5% (P=.07)</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Dellinger RP. Crit Care Med 2013;41:580-637*
## Hospital Mortality by Time to Antibiotics

<table>
<thead>
<tr>
<th>Time to ABX(^1), hrs</th>
<th>OR(^2)</th>
<th>95% CI</th>
<th>(p)-value</th>
<th>Probability of mortality(^3)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (ref)</td>
<td>1.00</td>
<td>---</td>
<td>---</td>
<td>18.7</td>
<td>17.5</td>
</tr>
<tr>
<td>1</td>
<td>1.05</td>
<td>1.02</td>
<td>1.07</td>
<td>19.3</td>
<td>18.3</td>
</tr>
<tr>
<td>2</td>
<td>1.09</td>
<td>1.04</td>
<td>1.15</td>
<td>20.0</td>
<td>19.1</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>1.06</td>
<td>1.23</td>
<td>20.8</td>
<td>19.7</td>
</tr>
<tr>
<td>4</td>
<td>1.19</td>
<td>1.08</td>
<td>1.32</td>
<td>21.5</td>
<td>20.3</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>1.11</td>
<td>1.41</td>
<td>22.3</td>
<td>20.7</td>
</tr>
<tr>
<td>6</td>
<td>1.31</td>
<td>1.13</td>
<td>1.51</td>
<td>23.1</td>
<td>21.2</td>
</tr>
</tbody>
</table>

\(^1\) Time to ABX is based on 15,948 observations that are greater than or equal to zero

\(^2\) Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)
Recommendation #7: Antibiotics

- We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (Grade 1B).
- The antimicrobial regimen should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, and to reduce costs (Grade 1B).
- Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient’s presenting illness and local patterns of infection.
- We suggest combination empiric therapy for neutropenic patients with severe sepsis (Grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (Grade 2B).
Recommendation #8: Procalcitonin

- We suggest the use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection (Grade 2C).

- Procalcitonin levels are NOT recommended as a biomarker for the diagnosis of sepsis.
Recommendation #8: Procalcitonin Meta-Analysis

• Meta-analysis: 7 studies; 1075 pts with severe sepsis or septic shock

• No difference in hospital mortality and 28-day mortality

• Duration of antimicrobial therapy was significantly reduced in favor of procalcitonin-guided therapy (HR 1.27 [1.01-1.53], p<0.05)

Prkno et al, Critical Care 2013; 17: R291
Recommendation #9: Source Control

• We recommend that a specific anatomical diagnosis of infection requiring consideration for emergent source control (e.g., necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hours after the diagnosis is made, if feasible (Grade 1C).

• We suggest that when infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (Grade 2B).
  • The two Danish trials.
Recommendation #9: Source Control

- When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (Ungraded).

- If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (Ungraded).
Recommendation #10: Corticosteroids

- Corticosteroids only for vasopressor refractory shock
- Hydrocortisone 200 mg daily +/- fludrocortisone
- CORTICUS no difference in 28-day mortality
  - Earlier reversal of shock with hydrocortisone
- No adrenal axis testing recommended
- Taper steroids upon discontinuation of pressors
- Do **NOT** give steroids in the absence of shock
Recommendation #11: Blood Products

- PRBCs for Hg < 7 g/dL
- No FFP to correct INR unless procedures to be done
- No anti-thrombin III
- Platelets only if <10K, or <20K with “significant risk of bleeding, or >50K for invasive procedures
Recommendation #12: Glucose Control

- We recommend protocolized approach to blood glucose management, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL.

- This protocolized approach should target upper blood glucose <180 mg/dL rather than <110 mg/dL (Grade 1A).

  Great lesson in knowing patient population being studied and not making broad application!

Dellinger et al. *Intensive Care Med.* 2013;39:165-228
Glycemic Control: The van den Berghe Studies at a glance

2001

2006
Glycemic Control: NICE SUGARS

Mortality rates were 27.5% in the intensive-control group and 24.9% in the conventional-control group.

Excess mortality with intensive therapy due to cardiac death
Recommendation #13: Bicarbonate

- We recommend **against the use of sodium bicarbonate therapy** for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (Grade 2B).

- *For me, I would choose to paralyze a patient with cisatracurium BEFORE using bicarbonate therapy to decrease CO2 production*
## Compliance with Guidelines - Outcomes

### Table 3: Hospital mortality across low- and high-compliance sites for resuscitation management bundles

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low compliance</th>
<th>High compliance</th>
<th>Total</th>
<th>( \rho^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total ((n))</td>
<td>Died ((n))</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>11,609</td>
<td>4,475</td>
<td>38.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Location of severe sepsis identification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>5,984</td>
<td>1,850</td>
<td>30.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ward</td>
<td>3,970</td>
<td>1,800</td>
<td>45.3</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>1,655</td>
<td>825</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>Site duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>4,960</td>
<td>1,896</td>
<td>38.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 to &lt;3 years</td>
<td>1,611</td>
<td>600</td>
<td>37.2</td>
<td></td>
</tr>
<tr>
<td>≥3 years</td>
<td>5,038</td>
<td>1,979</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>Low management compliance</td>
<td>High management compliance</td>
<td>Total</td>
<td>( \rho^a )</td>
</tr>
<tr>
<td></td>
<td>Total ((n))</td>
<td>Died ((n))</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>13,813</td>
<td>4,611</td>
<td>33.8</td>
<td>0.038</td>
</tr>
<tr>
<td>Location where severe sepsis identified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>7,958</td>
<td>2,127</td>
<td>26.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ward</td>
<td>4,219</td>
<td>1,737</td>
<td>41.2</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>1,636</td>
<td>747</td>
<td>45.7</td>
<td></td>
</tr>
<tr>
<td>Site duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>5,103</td>
<td>1,766</td>
<td>34.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 to &lt;3 years</td>
<td>2,524</td>
<td>894</td>
<td>35.4</td>
<td></td>
</tr>
<tr>
<td>≥3 years</td>
<td>6,186</td>
<td>1,951</td>
<td>31.5</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Keys to Management

- Early identification with high index of suspicion
- Aggressive fluid resuscitation EARLY
  - Don’t stop even after starting vasopressors if fluid responsive!
- Best standard resuscitation directed towards restoration of perfusion and lactate clearance is equivalent to EGDT
- Early, appropriate and broad antimicrobial therapy
  - ONLY error is not to give them (assuming no allergies)
- Least invasive source control within 12 hours
Conclusions: Keys to Management

- Use procalcitonin to guide de-escalation and NOT to diagnose severe sepsis/septic shock
- Low dose corticosteroids ONLY with vasopressor refractory shock
- Avoid intensive glycemic control; keep glucose <180 g/dL
- ARDS Net Ventilation
QUESTIONS?