SEPSIS

Fawad Chaudry
`hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat' 

Niccolo Machiavelli (1469–1527)  
Reported in his book, The Prince, in 1513
Scheme of Presentation

- Key definitions
- Incidences
- Mortality
- Pathogenesis
- Treatment: early studies, follow up, recent guidelines
- Relevance to FRHS
Key Definitions

Sepsis
Severe Sepsis
Sepsis induced hypotension
Septic Shock
Multi Organ Dysfunction
Key Definitions

Sepsis

Severe Sepsis

Sepsis induced hypotension

Septic Shock

Multi Organ Dysfunction

Systemic Inflammatory Response Syndrome (SIRS) is a syndrome that is the consequence of a dysregulated inflammatory response to an infectious or non-infectious insult.

• It can be due to and is often indistinguishable from early sepsis
• Source of sepsis should be sought when it is suspected
# Key Definitions

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Multi Organ Dysfunction

### Systemic Inflammatory Response Syndrome (SIRS)

The Systemic Inflammatory Response Syndrome (SIRS) is a syndrome that is the consequence of a dysregulated inflammatory response to an infectious or non-infectious insult.

- It can be due to and is often indistinguishable from early sepsis
- Source of sepsis should be sought when it is suspected

### TABLE 1. Diagnostic Criteria for Sepsis

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General variables</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>(&gt; 38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature</td>
<td>(&lt; 36°C)</td>
</tr>
<tr>
<td>Heart rate &gt; 90/min⁻¹ or more</td>
<td>than two so above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
<td></td>
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<tr>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td>Significant edema or positive</td>
<td>(&gt; 20 mL/kg over 24 hr)</td>
</tr>
<tr>
<td>fluid balance</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose</td>
<td>(&gt; 140 mg/dL or 7.7 mmol/L) in the absence of diabetes)</td>
</tr>
<tr>
<td><strong>Inflammatory variables</strong></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis (WBC count &gt; 12,000 µL⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt; 4000 µL⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Normal WBC count with greater</td>
<td>than 10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein</td>
<td>(&gt; two so above the normal value)</td>
</tr>
<tr>
<td>Plasma procalcitonin</td>
<td>(&gt; two so above the normal value)</td>
</tr>
<tr>
<td><strong>Hemodynamic variables</strong></td>
<td></td>
</tr>
<tr>
<td>Arterial hypotension (SBP &lt; 90 mm Hg, MAP &lt; 70 mm Hg, or an SBP decrease &gt; 40 mm Hg in adults or less than two so below normal for age)</td>
<td></td>
</tr>
<tr>
<td><strong>Organ dysfunction variables</strong></td>
<td></td>
</tr>
<tr>
<td>Arterial hypoxemia (Pao₂/Fio₂ &lt; 300)</td>
<td></td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt; 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)</td>
<td></td>
</tr>
<tr>
<td>Creatinine increase &gt; 0.5 mg/dL or 44.2 µmol/L</td>
<td></td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt; 1.5 or aPTT &gt; 60 s)</td>
<td></td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
<td></td>
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<tr>
<td>Thrombocytopenia (platelet count &lt; 100,000 µL⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt; 4 mg/dL or 70 µmol/L)</td>
<td></td>
</tr>
<tr>
<td><strong>Tissue perfusion variables</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperlactatemia (&gt; 1 mmol/L)</td>
<td></td>
</tr>
</tbody>
</table>
**Key Definitions**

- **Sepsis**
- **Severe Sepsis**
- **Septic Shock**
- **Multi Organ Dysfunction**

**SEVERE SEPSIS** refers to sepsis-induced tissue hypoperfusion or organ dysfunction with any of the following thought to be due to the infection:

- Sepsis-induced hypotension
- Lactate above upper limits of laboratory normal
- Urine output <0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation
- Acute lung injury with PaO2/FIO2 <250 in the absence of pneumonia as infection source
- Acute lung injury with PaO2/FIO2 <200 in the presence of pneumonia as infection source
- Creatinine >2 mg/dL
- Bilirubin >2 mg/dL
- Platelet count <100,000
- Coagulopathy (INR >1.5)
Key Definitions

Sepsis

Severe Sepsis

Sepsis induced hypotension

Septic Shock

Multi Organ Dysfunction

Defined as a **Systolic Blood Pressure (SBP) < 90 mm Hg** or mean arterial pressure (MAP) < 70 mm Hg or a **SBP decrease > 40 mm Hg or less** than two standard deviations below normal for age in the absence of other causes of hypotension and.
Key Definitions

Sepsis
Severe Sepsis
Sepsis induced hypotension
Septic Shock
Multi Organ Dysfunction

**Sepsis-induced hypotension** persisting despite adequate fluid resuscitation, which may be defined as infusion of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent).
**Key Definitions**

**Sepsis**

**Severe Sepsis**

**Sepsis induced hypotension**

**Septic Shock**

**Multi Organ Dysfunction**

Progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention

- **Primary MODS** - Well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself (eg, renal failure due to rhabdomyolysis)

- **Secondary MODS** - Organ failure that is not in direct response to the insult itself, but is a consequence of the host’s response (eg, acute respiratory distress syndrome in patients with pancreatitis)
## DEFINING CRITERIA OF ACCP/SCCM NAMED CONDITIONS

<table>
<thead>
<tr>
<th>ACCP/SCCM named condition</th>
<th>Defining criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>Core body temperature $&gt;38^\circ C$ or $&lt;36^\circ C$ HR $\geq 90$ bpm&lt;br&gt;Respirations $\geq 20$/min (or $\text{PaCO}_2 &lt; 32$ mmHg) WBC $\geq 12,000/\mu l$ or $\leq 4000/\mu l$ or $&gt;10%$ immature forms</td>
</tr>
<tr>
<td>Sepsis</td>
<td>At least two SIRS criteria caused by known or suspected infection</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis with acute organ dysfunction (including hypoperfusion and hypotension) caused by sepsis</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Sepsis with persistent or refractory hypotension or tissue hypoperfusion despite adequate fluid resuscitation</td>
</tr>
<tr>
<td>MODS</td>
<td>The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention.</td>
</tr>
</tbody>
</table>
Figure 1. Relationship between systemic inflammatory response and infection, where the overlap indicates sepsis.
SIRS: Systemic inflammatory response syndrome.
RISK FACTORS

1. Bacteremia

2. Advanced age (>65 years)
   - An independent predictor of mortality due to sepsis.
   - Older adult non-survivors tend to die earlier during hospitalization
   - Older adult survivors more frequently require skilled nursing or rehabilitation after hospitalization

3. Immunosuppression

4. Diabetes and cancer
   - Alteration of immune system; Increase the risk of nosocomial sepsis

5. Community acquired pneumonia
   - Severe sepsis and septic shock develop in approximately 48 and 5 percent, respectively, of patients with community-acquired pneumonia

6. Genetic factors
INCIDENCE

• Sepsis may occur in between 6 and 30% of all intensive care unit (ICU) patients, with substantial variation due to the heterogeneity between ICUs [8]) (Crit. Care. Med 2006)

• In most developed countries, the incidence of severe sepsis has been identified as between 50 and 100 cases per 100,000 people in the population [10] (Curr. Infect. Dis. Resp 2005)

• In general, more than 50% of severe sepsis patients will require intensive care services

• The global prevalence of severe sepsis patients initially presenting with:
  – Either hypotension with lactate ≥ 4 mmol/L - 16.6%
  – Hypotension alone - 49.5%
  – Lactate ≥ 4 mmol/L alone - 5.4%
In the late 1970s, 164,000 annual cases of sepsis.

More recent estimates exceed 1,665,000 annual cases of sepsis.

In the United States between 2000 and 2009 hospital stays with:

- A principal diagnosis of septicemia increased 148 percent (10.6 percent annually).
- Secondary diagnoses of septicemia increased by only 66 percent (5.8 percent annually).
Trends in hospital stays with Septicemia 1993-2009

• A two-decade study of US hospitalizations identified an increase in the incidence of sepsis among hospitalized patients by 8.7% per year \((N. Engl. J. Med. 2003)\)

• A retrospective population-based analysis reported increased rates of sepsis and septic shock from 13 to 78 cases per 100,000 between 1998 and 2009 \((Crit. Care Med. 2013)\)

• At present, it is estimated that there are more than 1,000,000 cases of sepsis among hospitalized patients each year in the USA
MORTALITY

• From data extending back to 1979, the risk of dying with sepsis was near 30% in the early years, and since the year 2000 the risk has been under 20%

• Decreased mortality rate decreased due to:
  – Increased detection of early sepsis
  – compliance with practice guidelines

Mortality averaged 28 percent during the first six years of the study and 18 percent during the last six years. The bar represent the standard error. (N Engl Med 2003; 348:1546.)

• During the study period 3708 patients were admitted to the survey units, and 2527 (68%) met the criteria for SIRS

• Among patients with SIRS:
  – 649 (26%) developed sepsis
  – 467 (18%) developed severe sepsis
  – 110 (4%) developed septic shock.

• Stepwise increases in mortality rates in the hierarchy from SIRS, sepsis, severe sepsis, and septic shock: 7%, 16%, 20%, and 46%, respectively
• The mortality rate
  
  • In septic patients with both hypotension and lactate \( \geq 4\) mmol/L - 46.1%
  
  • In severely septic patients:
    
    – With hypotension alone - 36.7%
    
    – Lactate \( \geq 4\) mmol/L alone - 30%

  (Crit Care Med 2010)

• Increased mortality associated with bloodstream infections due to:
  
  • Methicillin-resistant staphylococcus aureus (odds ratio 2.70, 95% CI 2.03-3.58)
  
  • Non-candidal fungus (odds ratio 2.66, 95% CI 1.27-5.58)
  
  • Candida (odds ratio 2.32 95% CI 1.21-4.45)
  
  • Methicillin-sensitive staphylococcus aureus (odds ratio 1.9, 95% CI 1.53-2.36)
  
  • Pseudomonas (odds ratio 1.6, 95% CI 1.04-2.47), as well as polymicrobial infections (odds ratio 1.69, 95% CI 1.24-2.30)

(Crit Care Med 2006)
PATHOPHYSIOLOGY

- The balance of proinflammatory and antiinflammatory mediators regulates the inflammatory processes.
- Sepsis occurs when the release of proinflammatory mediators in response to an infection exceeds the boundaries of the local environment, leading to a more generalized response.
Potential outcomes of mediator release in sepsis

Insult
- Severe infection (sepsis)
- Other (SIRS)

Inflammation

Proinflammatory system

Cellular injury
MODS

Cellular repair
Recovery

Antiinflammatory system
PROGRESSION OF LOCALIZED INFECTION TO SEPSIS

Multifactorial

1. Microorganisms:
2. Excess proinflammatory markers (IL1, TNF alpha)
3. Complement activation
4. Genetic susceptibility - (SNPs)
Transition to MODS

• Tissue ischemia:
  a. **Microcirculatory lesions**
     1) Coagulation
     2) Fibrinolysis imbalance
  b. **Endothelial lesions**
     1) Increase in receptor-mediated neutrophil-endothelial cell adherence
     2) Reactive oxygen species,
     3) Vasoactive substances

• **Cytopathic injury** - mitochondrial damage and decreased ability to utilize oxygen

• Decreased apoptosis of pro inflammatory cells
MOD

- Apoptosis
- Direct cellular damage (cytokines, neutrophils, pathogens)
- Microvascular thrombosis
- Tissue hypoperfusion/hypoxia
- Mitochondrial dysfunction
Evolution of Pathogens

• From 1979 through 1987, gram-negative bacteria were the predominant organisms causing sepsis, whereas gram-positive bacteria were reported most commonly in each subsequent year.

• Among the organisms reported to have caused sepsis in 2000:
  – Gram-positive bacteria 52.1 percent of cases
  – Gram-negative bacteria 37.6 percent
  – Polymicrobial infections 4.7 percent
  – Anaerobes 1.0 percent
  – Fungi for 4.6 percent

• The number of cases of sepsis caused by fungal organisms increased by 207 percent, from 5231 cases in 1979 to 16,042 cases in 2000.

![Graph showing the number of cases of sepsis for Gram-negative bacteria, Gram-positive bacteria, and fungi from 1979 to 2001.](image)
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK (N Engl J Med 2001)

• Background: The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

• Methods:
  – Prospective, randomized study
  – Patients at urban emergency room assigned to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the ICU.
  – Clinicians were blinded to the treatment assignment.
  – Following were compared made between study groups:
    • In-hospital mortality (the primary efficacy outcome)
    • End points with respect to resuscitation
    • Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours
  
• Patients followed for 60 days or until death
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Therapy (N=133)</th>
<th>Early Goal-Directed Therapy (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.4±17.1</td>
<td>67.1±17.4</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49.6</td>
<td>49.2</td>
</tr>
<tr>
<td>Male</td>
<td>50.4</td>
<td>50.8</td>
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<tr>
<td>Time from arrival at emergency department to enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (hr)</td>
<td>1.5±1.7</td>
<td>1.3±1.5</td>
</tr>
<tr>
<td>Median (min)</td>
<td>50.5</td>
<td>59.0</td>
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<tr>
<td>Entry criteria</td>
<td></td>
<td></td>
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<tr>
<td>Temperature (°C)</td>
<td>36.6±2.3</td>
<td>35.9±3.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>114±27</td>
<td>117±31</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109±34</td>
<td>106±36</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>30.2±10.6</td>
<td>31.8±10.8</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide (mm Hg)</td>
<td>30.6±15.1</td>
<td>31.5±15.7</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>14,200±9,600</td>
<td>13,600±8,300</td>
</tr>
<tr>
<td>Lactate (mmol/liter)</td>
<td>6.9±4.5</td>
<td>7.7±4.7</td>
</tr>
<tr>
<td>Baseline laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap (mmol/liter)</td>
<td>21.4±8.5</td>
<td>21.7±7.6</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.6±2.0</td>
<td>2.6±2.0</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>45.4±33.0</td>
<td>47.1±31.3</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.9±3.0</td>
<td>1.3±1.7</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (U/liter)</td>
<td>123±130</td>
<td>117±159</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.8±0.7</td>
<td>2.8±0.7</td>
</tr>
<tr>
<td>Chronic coexisting conditions (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>38.7</td>
<td>38.5</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>30.2</td>
<td>36.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>23.5</td>
<td>26.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease or emphysema</td>
<td>13.4</td>
<td>18.0</td>
</tr>
<tr>
<td>Condition</td>
<td>2012</td>
<td>2013</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.9</td>
<td>30.8</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>1.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66.4</td>
<td>68.4</td>
</tr>
<tr>
<td>Liver disease</td>
<td>23.5</td>
<td>23.1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>10.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>31.9</td>
<td>34.2</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>21.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>31.1</td>
<td>29.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis (%)†</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Medical condition</td>
<td>93.3</td>
<td>90.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>39.5</td>
<td>38.5</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>27.7</td>
<td>25.6</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Other</td>
<td>21.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Surgical condition</td>
<td>6.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intraabdominal process</td>
<td>5.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Abscess of the arms or legs</td>
<td>0.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Types and features of sepsis (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe sepsis</td>
<td>48.7</td>
<td>45.3</td>
</tr>
<tr>
<td>Septic shock</td>
<td>51.3</td>
<td>54.7</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>71.4</td>
<td>75.2</td>
</tr>
<tr>
<td>Culture positive</td>
<td>76.5</td>
<td>76.1</td>
</tr>
<tr>
<td>Culture negative</td>
<td>23.5</td>
<td>23.9</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>36.1</td>
<td>34.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic therapy</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Antibiotics given in the first 6 hr (%)</td>
<td>92.4</td>
<td>86.3</td>
</tr>
<tr>
<td>Antibiotics adequate (%)</td>
<td>94.3</td>
<td>96.7</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>11.3±15.8</td>
<td>11.7±16.2</td>
</tr>
</tbody>
</table>
Protocol for Early Goal Directed Therapy

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

- < 8 mm Hg
  - Crystalloid
  - Colloid

- 8–12 mm Hg

MAP

- < 65 mm Hg
  - Vasoactive agents

- > 90 mm Hg

ScvO₂

- < 70%
  - Transfusion of red cells until hematocrit ≥ 30%

- ≥ 70%
  - Inotropic agents

Goals achieved

- No

- Yes
  - Hospital admission
Overview of Patient Enrollment and Hemodynamic Support

SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter

Assessment and consent

Randomization

Standard therapy in emergency department (n=133)

Early goal-directed therapy (n=130)

Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization

CVP ≥8–12 mm Hg

MAP ≥65 mm Hg

Urine output ≥0.5 ml/kg/hr

Standard care

Hospital admission

CVP ≥8–12 mm Hg

MAP ≥65 mm Hg

Urine output ≥0.5 ml/kg/hr

ScvO2 ≥70%

SaO2 ≥93%

Hematocrit ≥30%

Cardiac index

VO2

Vital signs and laboratory data obtained every 12 hr for 72 hr

Did not complete 6 hr (n=14)

Follow-up

Did not complete 6 hr (n=13)
Treatments Administered

• During initial 6 hours:
  – EGDT group:
    • Received more Fluid (P<0.001)
    • Received more frequent red-cell transfusion (P<0.001) and inotropic support (P<0.001)
  – Similar proportions of patients in the two groups required vasopressors (P=0.62) and mechanical ventilation (P=0.90)

• During 7 to 72 hours:
  – Standard therapy group:
    • Received more fluid (P=0.01) and
    • Received more frequent red-cell transfusion (P<0.001)
    • Received more Vasopressors (P=0.03)
    • Underwent mechanical ventilation (P<0.001) and pulmonary-artery catheterization (P=0.04)
  – The rate of use of inotropic agents was similar in the two groups (P=0.14)
• **During 0 to 72 hours**

  No significant difference between the two groups:
  
  • In the total volume of fluid administered (P=0.73) or
  • the rate of use of inotropic agents (P=0.15)

  In Standard group:
  
  • Increase in: Vasopressors (P=0.02), mechanical ventilation (P=0.02) and underwent pulmonary-artery catheterization (P=0.01)
  • Smaller proportion required red-cell transfusion (P<0.001).

• **RESULTS:**

  In EGDT group:
  
  – In-hospital mortality was 30.5 % as compared to 46.5% in standard therapy  (P=0.009)
  
  – During the interval from 7 to 72 hours :
    
    • Higher mean (±SD) central venous oxygen saturation (70.4±10.7 percent vs. 65.3±11.4 percent)
    • Lower lactate concentration (3.0±4.4 vs. 3.9±4.4 mmol per liter)
    • Lower base deficit (2.0±6.6 vs. 5.1±6.7 mmol per liter)
    • Higher pH (7.40±0.12 vs. 7.36±0.12)
    • Lower Mean APACHE II scores were (13.0±6.3 vs. 15.9±6.4, P<0.001).
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 (46.5)</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>

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.
†Percentages were calculated by the Kaplan–Meier product-limit method.
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.
CONCLUSION

Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.
Early interventions in severe sepsis and septic shock: a review of the evidence one decade later
(Minerva Anestesiol 2012;78:712-24)

- A comprehensive approach to the first 6 hours of sepsis management which is commonly referred to as the resuscitation bundle (RB)
- The RB consists of early diagnosis, risk stratification using lactate levels, hemodynamic response after a fluid challenge, antibiotics, source control and hemodynamic optimization or EGDT
- Examined one decade of evidence for the components of the RB examining its impact on systemic inflammation, the progression of organ failure, healthcare resource consumption and mortality in severe sepsis and septic shock
Early Goal Directed therapy Algorithm

Suspected infection and Document Source within 2 hours

Risk Stratification:
- Systolic blood pressure < 90 mmHg after 20-40 cc/kg volume challenge or
- Lactic acid > 4 mmole/liter

Antibiotics within 1 to 3 hours and Source Control

CVP
- < 8 mmHg → Crystalloid or Colloid
- > 8-12 mmHg
- >65-90 mmHg

MAP
- < 65 or > 90 mmHg → Vasoactive Agent(s)

ScvO₂
- < 70%
- > 70%

Goals Achieved

Decrease oxygen consumption:
- Sedation and Mechanical Ventilation

SaO₂ > 93%
- Packed red blood cells to Hct > 30%

Inotrope (s)
Comprise over 50 publications containing over 18,000 adult patient

**Table I.** — Comparison of sepsis intervention studies using the resuscitation bundle compared to the original EGDT study. 8, 41, 49, 68, 80-128

<table>
<thead>
<tr>
<th>Summary of implementation study</th>
<th>Rivers et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before or control</td>
</tr>
<tr>
<td>Number of patients</td>
<td>9527</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>24.2</td>
</tr>
<tr>
<td>Sex, % Males</td>
<td>58.15</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8</td>
</tr>
<tr>
<td>Mortality before (SD)**</td>
<td>46.8 (26)%</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>0.37</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>18.3%</td>
</tr>
<tr>
<td>NNT</td>
<td>5.45</td>
</tr>
</tbody>
</table>

*Includes before and after and concurrent implementation studies. **The average mortality of each study. NNT = number needed to treat.
Health care Consumption

- The associated cost for sepsis in the United States:
  - Approaches over $ 50 billion per year OR
  - 2.5% of the health care expenditure
  - Most expensive disease treated in hospital since 1997.

  (Healthcare Cost and Utilization Project. [cited 2012 April)

- EGDT has been shown to decrease hospital related costs consistently by 20%.139, 140

- The cost savings are largely driven by a significant decrease in hospital length of stay by five days per patient.141
Health care Consumption

- Coba et al. examined the impact of compliance with the goals of EGDT on patient outcomes when completed beyond the six-hour recommendation period.
- At 18 h: EGDT had an absolute 10.2% lower in-hospital mortality compared to the non-compliers (37.1% vs. 47.3%).
- When adjusted for differences in baseline illness severity, the compliers at 18 h had a greater reduction in predicted mortality of 26.8% versus 9.4% (P<0.01).

(J Intensive Care Med 2011)
Early Goal Directed Therapy

Decreases mortality (16-18%)
Decreases the progression of organ failure
  - Decreases the progression of acute kidney injury
  - Decreases need for mechanical ventilation
Modulates the early inflammatory response
Decreases health care costs (20%)
  - Decreased duration of mechanical ventilation
  - Decreased hospital length of stay
Is effective up to 18 hours after disease onset (in the ED and ICU)
Decreases sudden cardiopulmonary complications
Is effective in community and tertiary care hospitals

**Diagnostic components (associated with increased mortality):**
  - Lactate > 4 mm/L
  - Systolic blood pressure <90 mmHg

**Components (associated with improved outcomes):**
  - Antibiotics within 1 to 3 hours
  - CVP >8 mmHg
  - MAP >65 mmHg
  - Hematocrit >30%
  - ScvO$_2$ >70%
    - Threshold for red blood cell transfusion
    - Need for inotropic therapy
    - Indication for and response to mechanical ventilation
    - Is not equivalent to lactate clearance
SURVIVING SEPSIS CAMPAIGN GUIDELINES
FOR
MANAGEMENT OF SEVERE SEPSIS
AND SEPTIC SHOCK
In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock for practical use for bedside clinician.

Well known to be ‘SURVIVING SEPSIS CAMPAIGN’

2004; 2008; 2012
Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Bananchoche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Surviving Sepsis Campaign:
International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Andrew Rhodes, MB BS; Djillali Annane, MD; Herwig Gerlach, MD, PhD; Steven M. Opal, MD; Jonathan E. Sevransky, MD; Charles L. Sprung, MD; Ivor S. Douglas, MD; Roman Jaeschke, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nunnally, MD; Sean R. Townsend, MD; Konrad Reinhart, MD; Ruth M. Kleinpell, PhD, RN-CS; Derek C. Angus, MD, MPH; Clifford S. Deutschman, MD, MS; Flavia R. Machado, MD, PhD; Gordon D. Rubenfeld, MD; Steven A. Webb, MB BS, PhD; Richard J. Beale, MB BS; Jean-Louis Vincent, MD, PhD; Rui Moreno, MD, PhD; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*
Surviving Sepsis Campaign 2012

• **Objective:** To provide an update to the “Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock,” last published in 2008.

• **Design:** A consensus committee of 68 international experts representing 30 international organizations. Stand-alone meeting, Teleconferences and electronic-based discussions

• **Methods:** Followed the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2)
Determination of Quality of Evidence

Underlying methodology
A (high) RCTs
B (moderate) Downgraded RCTs or upgraded observational studies
C (low) Well-done observational studies with control RCTs
D (very low) Downgraded controlled studies or expert opinion based on other evidence

Factors that may decrease the strength of evidence
1. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias
2. Inconsistency of results, including problems with subgroup analyses
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Main factors that may increase the strength of evidence
1. Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradient
<table>
<thead>
<tr>
<th>What Should be Considered</th>
<th>Recommended Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>High or moderate evidence</td>
<td>The higher the quality of evidence, the more likely a strong recommendation.</td>
</tr>
<tr>
<td><em>(Is there high or moderate quality evidence?)</em></td>
<td></td>
</tr>
<tr>
<td>Certainty about the balance of benefits vs. harms and burdens</td>
<td>The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.</td>
</tr>
<tr>
<td><em>(Is there certainty?)</em></td>
<td></td>
</tr>
<tr>
<td>Certainty in or similar values</td>
<td>The more certainty or similarity in values and preferences, the more likely a strong recommendation.</td>
</tr>
<tr>
<td><em>(Is there certainty or similarity?)</em></td>
<td></td>
</tr>
<tr>
<td>Resource implications</td>
<td>The lower the cost of an intervention compared to the alternative and other costs related to the decision—i.e., fewer resources consumed—the more likely a strong recommendation.</td>
</tr>
<tr>
<td><em>(Are resources worth expected benefits?)</em></td>
<td></td>
</tr>
</tbody>
</table>
MANAGEMENT OF SEVERE SEPSIS/SEPTIC SHOCK

GUIDELINES
INITIAL RESUSCITATION

• Recommend protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion
  – Should be initiated without any delay pending ICU admission.

• Goals (grade 1C):
  a) CVP 8–12 mm Hg
  b) MAP ≥ 65 mm Hg
  c) Urine output ≥ 0.5 mL/kg/hr
  d) Superior vena cava oxygenation saturation (Scvo2) or mixed venous oxygen saturation (SvO2) 70% or 65%, respectively.

• Suggest targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (grade 2C).
RATIONALE

- Randomized, controlled, single-center study showed early quantitative resuscitation improved survival for emergency department patients presenting with septic shock with a 15.9% absolute reduction in 28-day mortality.


- A multicenter trial (n=314) with severe sepsis in eight Chinese centers reported a 17.7% absolute reduction in 28-day mortality. Survival rates = 75.2% vs. 57.5% (p=0.001)

(Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2010; 6:331–334)
Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial  (JAMA 2010)

- Multicenter randomized, noninferiority trial involving patients with severe sepsis and evidence of hypoperfusion or septic shock who were admitted to the emergency department from January 2007 to January 2009 at 1 of 3 participating US urban hospitals.

- Randomly assigned patients to 1 of 2 resuscitation protocols
  - ScvO2 group (n=150): Resuscitated to normalize central venous pressure, mean arterial pressure and ScvO2 of at least 70%
  - Lactate clearance group (n=150): Resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%

- Primary outcome - absolute in-hospital mortality rate; Noninferiority threshold set at −10%

- RESULTS:
  - In ScvO2 group: 34 patients (23%) died while in the hospital (95% confidence interval [CI], 17%–30%)
  - In the lactate clearance group: 25 patients died (17%; 95% CI, 11%–24%)
  - Observed difference between mortality rates did not reach the predefined −10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, −3% to 15%).
  - No differences in treatment-related adverse events between the groups.
Early Lactate-Guided Therapy in Intensive Care Unit Patients A Multicenter, Open-Label, Randomized Controlled Trial

- 348 patients with lactate levels ≥ 3 mmol/L.

- With greater than or equal to 20% decrease in lactate levels per 2 hrs of the first 8 hrs in addition to ScvO2 target achievement:

  9.6% absolute reduction in mortality (p = 0.067; adjusted hazard ratio, 0.61; 95% CI, 0.43–0.87; p = 0.006).

(Am J Respir Crit Care Med 2010; 182:752–761)
Lactate Normalization vs SCVO2

- However patients included by Jones et al had lower illness severity, had lower lactate levels, more frequently in vasodilatory shock and less mechanically ventilated.
- Only 30 interventions in 10% of patients
- 20-50% of septic shock patients will never elevate lactate levels at presentation or during their clinical course
- These observations indicate that using lactate and SCVO2 are complementary end points but not mutually exclusive
SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1) Recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (Grade 1C)

2) Performance improvement efforts in severe sepsis should be used to improve patient outcomes (UG)
The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. (Crit. Care Med. 2010)

- Elements of the guidelines were "bundled" into two sets of targets to be completed within 6 hrs and within 24 hrs. An analysis was conducted on data submitted from January 2005 through March 2008.
- Data from 15,022 subjects at 165 sites were analyzed to determine the compliance with bundle targets and association with hospital mortality.

Results:

- Compliance:
  - Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 yrs (p < .0001).
  - Compliance with the entire management bundle started at 18.4% in the first quarter and increased to 36.1% by the end of 2 yrs (p = .008).
  - Compliance with all bundle elements increased significantly, except for inspiratory plateau pressure, which was high at baseline.
- Mortality difference:
  - Unadjusted hospital mortality decreased from 37% to 30.8% over 2 yrs (p = .001).
  - The adjusted odds ratio for mortality improved the longer a site was in the Campaign, resulting in an adjusted absolute drop of 0.8% per quarter and 5.4% over 2 yrs (95% confidence interval, 2.5-8.4).
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 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 ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation)
   to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure 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.
Recommendations

DIAGNOSIS

1. Recommend cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C).

2. At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).

RATIONALE:

- Vascular access device is the source of the infection if vascular access device is positive much earlier than the peripheral blood culture (With equivalent volumes of blood drawn for culture) i.e >2 hrs earlier
  

- The volume of blood drawn with the culture tube should be ≥ 10 mL
  

- The Gram stain and culture can be useful for respiratory tract specimens to determine presence of inflammatory cells are present (>5 PMNL/high-powered field and < 10 squamous cells/low-powered field).
  
  (Crit Care Med 2013)
Suggest use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection

RATIONALE:

– Tests have shown positive results significantly earlier than standard culture methods


– False-positive reactions can occur with colonization alone

  – Diagnostic utility in managing fungal infection in the ICU needs additional study

  *(J Clin Microbiol 2004)*

Recommend imaging studies performed promptly to confirm a potential source of infection (UG)
ANTIMICROBIAL THERAPY

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.

RATIONALE:

Number of studies showed measurable increased mortality with each hour delay in effective antibiotics

ANTIMICROBIAL THERAPY

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human shock (Crit Care Med, 2006)

- A retrospective cohort study performed between July 1989 and June 2004.
- 14 intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States
- Reviewed medical records of 2,731 adult patients with septic shock
- Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%.
- Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%
- By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12-2.48).
Recommem 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).

- **Candida** Risk factors: Immunosuppression, prior intense antibiotics, colonization in multiple sites.
- Recent Infectious Diseases Society of America (IDSA) guidelines recommend either fluconazole or an echinocandin.
- Empiric use of an echinocandin is preferred in patients recently been treated with antifungal agents, or if Candida glabrata infection is suspected from earlier culture data.

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).
ANTIMICROBIAL THERAPY

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).

RATIONALE:

– There is published literature relating to the use of procalcitonin as a tool to discontinue unnecessary antibiotics

– No evidence demonstrates that this practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic-related diarrhea from C. difficile

– Further research is necessary before the wide adoption of this strategy

(ANTIMICROBIALS Lancet Infect Dis 2007, Crit Care Med 2011)
**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.

- 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 Pseudomona spp. (grade 2B).

- For selected patients with severe infections associated with **respiratory failure and septic shock**, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is suggested for P. aeruginosa bacteremia (grade 2B)

- Combination of beta-lactam and a macrolide is suggested for patients with **septic shock from bacteremic Streptococcus pneumoniae** infections (grade 2B).
Suggest that combination therapy, when used empirically in patients with severe sepsis, should not be administered for longer than 3 to 5 days.

– De-escalation to the most appropriate single-agent therapy should be performed as soon as the susceptibility profile is known (grade 2B).

– Exceptions include:
  » Aminoglycoside monotherapy, which should be generally avoided, particularly for P. aeruginosa sepsis
  » Selected forms of endocarditis, where prolonged courses of combinations of antibiotics are warranted

Suggest that the duration of therapy typically be 7 to 10 days if clinically indicated (Grade 2C)

– Longer courses may be appropriate in patients with:
  – slow clinical response
  – Undrainable foci of infection
  – Bacteremia with S. aureus
  – Some fungal and viral infections,
  – Immunologic deficiencies, including neutropenia
ANTIMICROBIAL THERAPY

Suggest that antiviral therapy be initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C)

RATIONALE:

Recommendations for antiviral treatment include the use of:

- Early antiviral treatment of:
  - suspected or confirmed influenza among persons with severe influenza (who have require hospitalization)
  - suspected or confirmed influenza among persons at higher risk for influenza complications
  - therapy with a neuraminidase inhibitor (oseltamivir or zanamivir) for persons with influenza caused by 2009 H1N1 virus, influenza A (H3N2) virus, or influenza B virus, or when the influenza virus type or influenza A virus subtype is unknown

- CMV:
  - Active CMV viremia common (15%-35%) in critically ill patients;
  - Presence of CMV in the bloodstream- poor prognostic indicator
  - Whether CMV simply is a marker of disease severity or if the virus actually contributes to organ injury and death in septic patients ?(103).
  - No treatment recommendations can be given based on the current level of evidence.

SOURCE CONTROL

- A specific anatomical diagnosis of infection requiring consideration for emergent source control (eg, necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction):
  - Sought and diagnosed
  - Intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

- 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)
**SOURCE CONTROL**

- 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 (UG).

- 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) (UG).
INFECTION CONTROL

- Suggest introduction and investigation of selective oral decontamination (SOD) and selective digestive decontamination (SDD)
- And implementation if found effective to reduce the incidence of ventilator-associated pneumonia (VAP) (grade 2B)
- Suggest oral chlorhexidine gluconate (CHG) be used as a form of oropharyngeal decontamination to reduce the risk of VAP in ICU patients with severe sepsis (grade 2B).

RATIONALE:

- The efficacy of SDD, its safety, propensity to prevent or promote antibiotic resistance, and cost-effectiveness remain debatable despite a number of favorable meta-analyses and controlled clinical trials
- The data indicate an overall reduction in VAP but no consistent improvement in mortality, except in selected populations in some studies

(Cochrane Collaboration 2010: 9:1–72)
HEMODYNAMIC SUPPORT AND ADJUNCTIVE THERAPY

- **Crystalloids as the initial fluid of choice** in the resuscitation of severe sepsis and septic shock (grade 1B).

- **Against the use of hydroxyethyl starches** for fluid resuscitation of severe sepsis and septic shock (grade 1B).

- **Albumin in the fluid resuscitation of severe sepsis and septic shock** when patients require substantial amounts of crystalloids (grade 2C).
Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

- Prospective, multicenter, active-controlled, double-blind, randomized study in intensive care units
- Compared the hemodynamic efficacy and safety of 6% HES 130/0.4 and NaCl 0.9% for hemodynamic stability (HDS) in patients with severe sepsis.
- RESULTS:
  - Mortality rate:
    - Until Day 28
      - For HES group: 31/100 (31.0%)
      - For NaCl group: 24/95 (25.3%) (P = 0.37).
    - Until Day 90: Similar between treatments; No treatment effect on mortality rate detected (40/99 [40%] vs. 32/95 [34%]) for HES and NaCl, respectively (P = 0.33).
  1. Significantly less HES was used to reach HDS
    - With HES: 1,379 ± 886 ml
    - With NaCl group: 1,709 ± 1,164 ml [mean difference = -331 ± 1,033, 95% CI -640 to -21], P = 0.0185)
  2. Time to reach HDS: With HES was 11.8 ± 10.1 hours; With NaCl group: 14.3 ± 11.1 hours
  3. Acute renal failure occurred in 24 (24.5%) and 19 (20%) patients for HES and NaCl, respectively (P = 0.454)
Comparing the effect of hydroxyethyl starch 130/0.4 with balanced crystalloid solution on mortality and kidney failure in patients with severe sepsis (6S - Scandinavian Starch for Severe Sepsis/Septic Shock trial): Study protocol, design and rationale for a double-blinded, randomized clinical trial

- 6S trial randomised 800 patients with severe sepsis in 30 Scandinavian ICUs to masked fluid resuscitation using either 6% HES 130/0.4 in Ringer's acetate or Ringer's acetate alone

- **Primary Outcome**: Composite endpoint of 90-day mortality or end-stage kidney failure

- **Secondary Outcome**: severe bleeding or allergic reactions, organ failure, acute kidney failure, days alive without renal replacement therapy or ventilator support and 28-day and 1/2- and one-year mortality.

- **RESULTS**:
  - In septic patients (6S Trial Group) showed increased mortality rates with 6% HES 130/0.42 fluid resuscitation compared to Ringer's acetate
    
    51% vs. 43% (p = 0.03)
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care-The CHEST Study (N Engl J Med 2012)

- Randomly assigned (n=7000) patients admitted to an ICU in a 1:1 ratio to receive either 6% HES with a molecular weight of 130 kD and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization.

- Primary outcome: death within 90 days

- Secondary outcomes: Acute kidney injury and failure and treatment with renal-replacement therapy.

RESULTS:
- In the HES group: 597 of 3315 patients (18.0%) died within 90 days after randomization
- In normal Saline group: 566 of 3336 patients (17.0%) died (relative risk in the HES group, 1.06; 95% confidence interval [CI], 0.96 to 1.18; P = 0.26)
- No significant difference in the probability of survival between the HES group and the saline group during the 90 days after randomization (P = 0.27)
- Renal-replacement therapy was administered to 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 patients (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P = 0.04)

- Conclusion:
  - No significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline
  - More patients who received resuscitation with HES were treated with renal-replacement therapy
The evidence of harm observed in the 6S and CHEST studies and the meta-analysis (56 randomized trials) supports a high-level recommendation advising against the use of HES solutions in patients with severe sepsis and septic shock particularly since other options for fluid resuscitation exist.
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. The SAFE Study Investigators

- The SAFE study indicated that albumin administration was safe and equally as effective as 0.9% saline
- Patients (in ICU) randomly assigned to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the 28 days.
- Primary outcome measure: Death from any cause during the 28-day period after randomization.
- 6997 patients underwent randomization: 3497 assigned to receive albumin and 3500 to receive saline
- RESULTS:
  - 726 deaths in the albumin group vs 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87).
  - Similar proportion of patients with new single-organ and multiple-organ failure (P=0.85)
  - No difference in length of hospital and ICU stay, days on mechanical ventilation or days of renal replacement therapy
- Conclusion: In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.
A meta-analysis aggregated data from 17 randomized trials (n = 1977) of albumin vs. other fluid solutions in patients with severe sepsis/septic shock (130):

- 279 deaths occurred among 961 albumin-treated patients vs. 343 deaths among 1016 patients treated with other fluids.

Thus favoring albumin (odds ratio [OR], 0.82; 95% CI, 0.67−1.00; I² = 0%).

Comparison of albumin-treated patients with those receiving crystalloids (seven trials, n = 1441), showed: significantly reduced OR of dying for albumin-treated patients (OR, 0.78; 95% CI, 0.62−0.99; I² = 0%).

(Crit Care Med 2011)
• **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).

• **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 (UG)
VASOPRESSORS

Vasopressor therapy initially target a MAP of 65 mm Hg (grade 1C).

RATIONALE:

• The titration of norepinephrine to a MAP as low as 65 mm Hg has been shown to preserve tissue perfusion (134)

• The consensus definition of sepsis-induced hypotension for use of MAP in the diagnosis of severe sepsis is different (MAP < 70 mm Hg) from the evidence-based target of 65 mm Hg used in this recommendation
**Vasopressors**

- **Norepinephrine** as the first choice vasopressor (grade 1B).

- **Epinephrine** (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).

- **Vasopressin 0.03 units/minute** can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).

- **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) (UG).
**Recommendations**

**VASOPRESSORS**

- Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).

- Phenylephrine is not recommended in the treatment of septic shock except in circumstances where

  (a) norepinephrine is associated with serious arrhythmias

  (b) cardiac output is known to be high and blood pressure persistently low

  (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
**VASOPRESSORS**

- Information from five randomized trials (n = 1993 patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock


- A recent meta-analysis showed dopamine association with an increased risk (RR, 1.10 [1.01-1.20]; p = 0.035); in the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (RR, 2.34 [1.46-3.77]; p = 0.001)

  (Crit Care Med 2012)
### Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative Comparative Risks&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative Effect&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>No. of Participants (Studies)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Comments&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed Risk</td>
<td>Corresponding Risk</td>
<td>RR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term mortality</td>
<td>Dopamine 530 per 1000</td>
<td>Norepinephrine 482 per 1000 (440 to 524)</td>
<td>0.91 (0.83 to 0.99)</td>
<td>2043 (6 studies)</td>
<td>oo oo oo oo oo moderate</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Dopamine 229 per 1000</td>
<td>Norepinephrine 82 per 1000 (34 to 195)</td>
<td>0.47 (0.38 to 0.58)</td>
<td>1931 (2 studies)</td>
<td>oo oo oo oo oo moderate</td>
</tr>
<tr>
<td>—Supraventricular arrhythmias</td>
<td>Dopamine 39 per 1000</td>
<td>Norepinephrine 15 per 1000 (8 to 27)</td>
<td>0.35 (0.19 to 0.66)</td>
<td>1931 (2 studies)</td>
<td>oo oo oo oo oo moderate</td>
</tr>
</tbody>
</table>
Recommendations

VASOPRESSORS

LOW DOSE DOPAMINE

- Recommend that low-dose dopamine not be used for renal protection (grade 1A)

RATIONALE:

- A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in:
  - Primary outcomes (peak serum creatinine, need for renal replacement, urine output, time to recovery of normal renal function) or
  - Secondary outcomes (survival to either ICU or hospital discharge, ICU stay, hospital stay, arrhythmias)

(Clinical Trials Group. Lancet 2000, Crit Care Med 2001)
VASOPRESSORS

Norepinehrine vs Epinephrine

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

Recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).
INOTROPIC THERAPY

• A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of
  – 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 MAP (grade 1C).

• Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B)
CORTICOSTEROIDS

• Not using intravenous hydrocortisone as a treatment of adult septic shock patients:
  – If adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability
  – If this is not achievable, suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
**French Multicenter RCT**

Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock (*JAMA, 2002*)

- Placebo-controlled, randomized, double-blind, parallel-group trial performed in 19 intensive care units in France from October 9, 1995, to February 23, 1999. (n=300)
- With vasopressor-unresponsive septic shock patients (hypotension despite fluid resuscitation and vasopressors for more than 60 mins)
  - Showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as postadrenocorticotropic hormone [ACTH] cortisol increase ≤ 9 μg/dL)

Two smaller RCTs also showed significant effects on shock reversal with steroid therapy (*Crit Care Med 1999, 1998*)
Hydrocortisone therapy for patients with septic shock (CORTICUS TRIAL)  
*(N Engl J Med 2008)*

- Multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days.

- **Primary outcome at 28 days**: death among patients who did not have a response to a corticotropin test.

- **RESULTS**:
  - Of the 499 patients - 233 (46.7%) No response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group)
  - At 28 days - no significant difference in mortality in the two study groups.
  - In the hydrocortisone group - shock reversed more quickly; more episodes of superinfection, including new sepsis and septic shock.
CORTICOSTEROIDS

Suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B)

- Random cortisol levels may still be useful for absolute adrenal insufficiency; however, for septic shock patients who suffer from relative adrenal insufficiency (no adequate stress response), random cortisol levels have not been demonstrated to be useful.

- Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).

- Clinicians taper the treated patient from steroid therapy when vasopressors are no longer required (grade 2D).

- When low-dose hydrocortisone is given, we suggest using continuous infusion rather than repetitive bolus injections (grade 2D).
CORTICOSTEROIDS

- A study revealed that there is no difference in outcome of septic shock patients if low-dose hydrocortisone is used for 3 or 7 days; hence, no recommendation can be given with regard to the optimal duration of hydrocortisone therapy (189).

- An inappropriately low random cortisol level (< 18 μg/dL) in a patient with shock would be considered an indication for steroid therapy along traditional adrenal insufficiency guidelines.

- A subanalysis of the CORTICUS trial (178) revealed that the use of etomidate before application of low-dose steroids was associated with an increased 28-day mortality rate

(IIntensive Care Med 2009)
Blood Product Administration

Once tissue hypoperfusion has resolved and in the absence of myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease

– Recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to $< 7.0 \text{ g/dL}$ to target a hemoglobin concentration of $7.0 \text{ to } 9.0 \text{ g/dL}$ in adults (grade 1B).

– Transfusion Requirements in Critical Care trial suggested that a hemoglobin level of $7 \text{ to } 9 \text{ g/dL}$, compared with $10 \text{ to } 12 \text{ g/dL}$, was not associated with increased mortality in critically ill adults

Blood Product Administration

- Not using erythropoietin as a specific treatment of anemia associated with severe sepsis (grade 1B)

- Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).

- Not using antithrombin for the treatment of severe sepsis and septic shock (grade 1B)
In patients with severe sepsis, **administer platelets prophylactically**

- when counts are $< 10,000$/mm³ (10 x 10⁹/L) in the absence of apparent bleeding.
- when counts are $< 20,000$/mm³ (20 x 10⁹/L) if the patient has a significant risk of bleeding.
- higher platelet counts ($\geq 50,000$/mm³ [50 x 10⁹/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).
Immunoglobulins

• Not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).

One larger multicenter RCT (n = 624) in adult patients and one large multinational RCT in infants with neonatal sepsis (n = 3493) (211) found no benefit for intravenous immunoglobulin (IVIG).

(The SBITS study. Crit Care Med 2007;
Selenium and APC

• Suggest not using intravenous selenium to treat severe sepsis (grade 2C).

History of Recommendations Regarding Use of Recombinant Activated Protein C (rhAPC)

A history of the evolution of SSC recommendations as to rhAPC (no longer available) is provided.
Mechanical Ventilation

- Target a tidal volume of 6mL/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs. 12 mL/kg)
- Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H2O (grade 1B).
- Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
- Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis-induced moderate or severe ARDS (grade 2C).
Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia (grade 2C).

Prone positioning be used in sepsis-induced ARDS patients with a Pao2/Fio2 ratio ≤ 100mm Hg in facilities that have experience with such practices (grade 2B).

That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30-45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
That a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria:

a) Arousable

b) hemodynamically stable (without vasopressor agents)

c) no new potentially serious conditions

d) low ventilatory and end-expiratory pressure requirements

e) low Fio2 requirements which can be met safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).

A paired spontaneous awakening trial combined with a spontaneous breathing trial decreased the duration of mechanical ventilation, length of ICU and hospital stay, and 1-year mortality.

*(Lancet 2008)*
Mechanical Ventilation

- **Against the routine use of the pulmonary artery catheter** for patients with sepsis-induced ARDS (grade 1A)

- **A conservative rather than liberal fluid strategy** for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C)

- In the absence of specific indications such as bronchospasm, **not using beta 2-agonists** for treatment of sepsis-induced ARDS (grade 1B)
Mechanical Ventilation

Rationale

• The largest trial of a volume- and pressure-limited strategy showed an absolute 9% decrease in all-cause mortality in patients with ARDS ventilated with tidal volumes of 6 mL/kg compared with 12 mL/kg of predicted body weight (PBW), and aiming for a plateau pressure ≤ 30 cm H2O (233)

• A meta-analysis using individual patient data showed no benefit in all patients with ARDS; however, patients with moderate or severe ARDS (Pao2/Fio2 ratio ≤ 200 mm Hg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not (JAMA 2010)

• One meta-analysis suggested potential benefits for prone positioning in patients with profound hypoxemia and PaO2/FIO2 ratio ≤ 100 mm Hg, but not in those with less severe hypoxemia (Intensive Care Med 2010)
Sedation, Analgesia, and Neuromuscular blockade in Sepsis

- Recommend that either continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (grade 1B).

- Recommend that NMBAs be avoided if possible in the septic patient without ARDS due to the risk of prolonged neuromuscular blockade following discontinuation (grade 1C).

- Suggest a short course of an NMBA (≤ 48 hours) for patients with early, sepsis-induced ARDS and Pao2/Fio2 < 150 mm Hg (grade 2C).
Rationale

- A recent randomized clinical trial of continuous infusions of cisatracurium in patients with early ARDS and a Pao2/Fio2 < 150 mm Hg showed
  - improved adjusted survival rates and more organ failure-free days without an increased risk in ICU-acquired weakness compared with placebo-treated patients (N Engl J Med 2010)
  - The investigators used a high fixed dose of cisatracurium without train-of-four monitoring
  - Although many of the patients enrolled into this trial appeared to meet sepsis criteria, it is not clear whether similar results would occur in sepsis patients
GLUCOSE CONTROL

- Recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL. (grade 1A)

- Recommend blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter (grade 1C).
Rationale

• One large RCT single-center trial in a predominantly cardiac surgical ICU demonstrated a reduction in ICU mortality with intensive intravenous insulin (Leuven protocol) targeting blood glucose to 80 to 110mg/dL \(^{(N	ext{ Eng}l	ext{ J Med} 2001)}\).

• A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU length of stay of more than 3 days in three medical ICUs and overall mortality was not reduced \(^{(N	ext{ Eng}l	ext{ J Med} 2006)}\).
**Intensive versus Conventional Glucose Control in Critically Ill Patients**

*NICE-SUGAR Study Investigators* (N Engl J Med 2009)

- Parallel-group, randomized, controlled trial involving adult medical and surgical patients admitted to the ICUs of 42 hospitals: 38 academic tertiary care hospitals and 4 community hospitals.

- Of the 6104 patients who underwent randomization:
  - 3054 were assigned to undergo intensive control
  - 3050 to undergo conventional control

- Primary end point as death from any cause within 90 days after randomization.

**RESULTS:**

- **Mortality:**
  - 829 patients (27.5%) in the intensive-control group
  - 751 (24.9%) in the conventional-control group (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02).

- **Severe hypoglycemia (blood glucose level, ≤40 mg/dL):**
  - In 206 of 3016 patients (6.8%) in the intensive-control group
  - 15 of 3014 (0.5%) in the conventional-control group (P<0.001).
Several medical organizations, including:
- American Association of Clinical Endocrinologists
- American Diabetes Association
- American Heart Association,
- American College of Physicians,
- Society of Critical Care Medicine
published consensus statements
target glucose levels between 140 and 180 mg/dL

Renal Replacement Therapy

• Suggest that continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure because they achieve similar short-term survival rates (grade 2B).

• Suggest the use of continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 2D)

RATIONALE:

– Most recent and largest RCT) enrolled 360 patients and found no significant difference in survival between the continuous and intermittent groups. Moreover, no evidence supports the use of continuous therapies in sepsis independent of renal replacement needs  (Lancet, 2006)
Renal Replacement Therapy

1. Two prospective studies reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion and no survival benefit (Am J Kidney Dis 2004, Nephrol Dial Transplant 2001)

2. Four other prospective studies did not find any significant difference in mean arterial pressure or drop in systolic pressure between the two methods (Ren Fail 2003, Nephrol Dial Transplant 2005, Lancet 2006, Intensive Care Med 1996)
**Bicarbonate**

- 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 $\geq 7.15$ (grade 2B)
Recommend patients with severe sepsis receive *daily pharmacoprophylaxis against venous thromboembolism (VTE)* (grade 1B).

- Should be accomplished with *daily subcutaneous low-molecular weight heparin (LMWH)* (grade 1B versus twice daily UFH, grade 2C versus three times daily UFH).

- If creatinine clearance is <30 mL/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).

- Suggest that patients with severe sepsis be treated with a combination of *pharmacologic therapy and intermittent pneumatic compression devices* whenever possible (grade 2C).
DVT

• Recommend that septic patients who have a contraindication to heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not receive pharmacoprophylaxis (grade 1B).

• Rather suggest they receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases, we suggest starting pharmacoprophylaxis (grade 2C).
Stress Ulcer Prophylaxis

1. Recommend that stress ulcer prophylaxis using H 2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).

2. Suggest the use of proton pump inhibitors rather than H2 receptor antagonists (H2RA) (grade 2C).

3. Suggest that patients without risk factors should not receive prophylaxis (grade 2B).
Nutrition

1. Suggest administering oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hrs after a diagnosis of severe sepsis/septic shock (grade 2C).

2. Suggest avoiding mandatory full caloric feeding in the first week, but rather suggest low-dose feeding (e.g., up to 500 kcal per day), advancing only as tolerated (grade 2B).

3. Suggest using intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).

4. Suggest using nutrition with no specific immunomodulating supplementation in patients with severe sepsis (grade 2C).
1. Recommend that goals of care and prognosis be discussed with patients and families (grade 1B).

2. Recommend that the goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B).

3. Suggest that goals of care be addressed as early as feasible, but no later than within 72 hrs of ICU admission (grade 2C).
Rationale

• The use of proactive family care conferences to identify advanced directives and treatment goals within 72 hrs of ICU admission;
  – Promotes communication and understanding between the patient’s family and the care team
  – Improves family satisfaction
  – Decreases stress, anxiety, and depression in surviving relatives

• Facilitates end-of-life decision making; and shortens length of stay for patients who die in the ICU

Evaluation for Severe Sepsis Screening Tool

Severe Sepsis = Infection + SIRS + Organ Dysfunction

1. Does the patient have a current presumed (based on signs/symptoms) or documented infection?  
   - Pneumonia  
   - Empyema  
   - Acute abdominal infection (e.g., peritonitis)  
   - Urinary tract infection  
   - Skin/soft tissue infection  
   - Endocarditis  
   - Bone/joint infection  
   - Bloodstream catheter infection  
   - Meningitis  
   - Wound infection  
   - Implantable device infection  
   - Other ____________  

   YES ____ NO ____  

   If any one of the above under #1 is present, select YES.

2. Are any two of the following signs & symptoms of infection both present and not considered to be chronic?  
   Note: Laboratory values may not be available. Solicit order from MD if needed.
   
   **SIRS Criteria**  
   - Hyperthermia > 100.4°F  
   - Hypothermia < 96.8°F  
   - Tachycardia > 90 bpm  
   - Tachypnea > 20 bpm  
   - Leukocytosis (WBC count > 12,000 cells/µL)  
   - Leukopenia (WBC count < 4,000 cells/µL)  

   YES ____ NO ____  

   If two or more of the above under #2 is present, select YES.

3. Are any of the following organ dysfunction criteria present and not considered to be chronic or a result of therapy?  
   - SBP < 90 mm Hg or MAP < 65 mm Hg  
   - SBP decrease > 40 mm Hg from baseline  
   - Bilateral pulmonary infiltrates with a new (or increased) oxygen requirement to maintain SpO2 > 90%  
   - Bilateral pulmonary infiltrates with PaO2/FIO2 ratio < 300  
   - Creatinine > 2.0 mg/dL or Urine output < 0.5 mL/kg/hour for > 2 hours  
   - Bilirubin > 2 mg/dL  
   - Platelet count < 100,000  
   - Coagulopathy (INR > 1.5 or PTT > 60 sec)  
   - Lactate > 2 mmol/L  

   YES ____ NO ____  

   If any one of the above under #3 is present, select YES.

---

If YES to all 3 items above, the patient meets the criteria for possible SEVERE SEPSIS. Consider transfer to IMCU/ICU.  
***If a positive screen call an RRT and/or notify the physician immediately.***

---

If the patient is discharged, the form will be sent to B. Miller at Med Staff via intercampus mail.

---

Physician notified of positive screen?  
Yes ___ Time: _______
No ___ Reason: ______
New Orders Received: _______
Transfer to ICU/IMCU Yes ___ No ___
Additional Fluid Bolus Yes ___ No ___

---

Signature: ____________  
Unit or Room: ________  
Date: ________  
Time: ________

---

**NOT A PERMANENT PART OF THE MEDICAL RECORD**

PATIENT STICKER
Initial Management of Patient with Severe Sepsis
Severe Sepsis = Infection + SIRS + Organ Dysfunction

Severe Sepsis & Septic Shock Resuscitation Goals in First 6 hours:
- Central Venous Pressure 8-13 mmHg
- Mean Arterial Pressure (MAP) ≥ 65
- Urine output ≥ 0.5 ml/kg/hr

<table>
<thead>
<tr>
<th>Time</th>
<th>Initial Labs Drawn (CBC, CMP, PT, PTT, INR, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood Cultures x 2</td>
</tr>
<tr>
<td></td>
<td>Serum Lactate</td>
</tr>
<tr>
<td></td>
<td>Calculate recommended initial fluid bolus: Pt's wt in kg ______ × 30 ml = ______ ml</td>
</tr>
<tr>
<td></td>
<td>Initial fluid bolus required if SBP &lt; 90 mmHg or MAP &lt; 65 mmHg, or Lactate &gt; 4</td>
</tr>
<tr>
<td></td>
<td>TOTAL FLUID INTAKE in ED or prior to ICU/IMCU or other admit = ______ ml</td>
</tr>
<tr>
<td></td>
<td>Repeat Fluid Bolus if SBP ≤ 90 or MAP ≤ 65</td>
</tr>
</tbody>
</table>

Antimicrobials: ____________________________

Started at ____________________________

IV administration within 1 hour of recognition of Septic Shock and severe sepsis without septic shock.

CVP catheter inserted. Insert CVP if MAP < 65 or SBP < 90 mmHg after initial fluid bolus, repeat Fluid bolus if CVP ≤ 8

Vasopressors: Norepinephrine (Levophed) as first choice with epinephrine added or potentially substituted when adequate blood pressure cannot be maintained. Phenylephrine not recommended except if norepinephrine is associated with serious arrhythmias, if cardiac output is high and blood pressure persistently low, or as salvage therapy when MAP target is not achieved.

Glucose Control: Goal < 180 mg/dl

---

SIRS Criteria + Infection &/or Positive Sepsis Screen

2 of 4 SIRS Criteria Present
- Monitor Closely.
- May admit to Regular Floor.

3-4 Positive SIRS Criteria & YES to #3 (Start from here)

Administer Crystalloid fluid bolus (30 ml/kg).

- Consider IMCU admit.
- Monitor closely for further s/s of developing sepsis

- Repeat MAP. If it ≤ 65

- Respiratory Failure

- Supplemental Intubation with mechanical ventilation (if necessary)

Sepsis-Induced Hypotension (clinical picture of sepsis + one or both of the following criteria):
1. Hypotension* AFTER initial fluid bolus (30 ml/kg)
2. Lactate > 4 mmol/L, with any BP

Yes

Yes

Insert CVP Call for ICU Bed

Yes

Continue Crystalloid resuscitation (30 ml/kg boluses)

Transfer to ICU Bed
<table>
<thead>
<tr>
<th>Quarter</th>
<th>Septic Shock</th>
<th>Mortality</th>
<th>Rate</th>
<th>Severe Sepsis</th>
<th>Mortality</th>
<th>Rate</th>
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**Sepsis Patients 2013**

- Septic Shock
- Severe Sepsis
- Sepsis

**Mortality Rate for All Sepsis Cases**

- Goal
- Year Mortality Rate

**Mortality Rate for All Sepsis Cases**

- Year 2011
- Year 2012
- Year 2013

**All Sepsis POE**

- ED
- ED MS
- From CAH Tx in ED
- Direct Admit
- Floor Dx
- Home

- POE:
  - 75%
  - 3%
  - 3%
  - 1%
  - 3%
  - 1%
process Trial

- Randomized 1341 patients with severe sepsis and septic shock.
  - Group 1: n=439. Protocol based EGDT with placement of central line and monitoring of SvO2 and CVP, Vasopressors, dobutamine and PRBC.
  - Group 2: n=446. Protocol based standard therapy. Defined as 6 hours protocol prompted resuscitation with IVF administration to clinical euvolemia and PRBC transfusion to goal Hg of 7.5. CVC and SvO2 not mandatory
  - Group 3: n=456. Bed side director provided all care without any prompted protocol
• **APACHE II** illness severity scores were ~21 in all groups.

• Central venous catheters were placed in 93.2% of patients in the EGDT group, 56.5% in the protocol-based standard therapy group and 57.9% in the usual care group. Similarly, ScVO2 was monitored in 93.6% patients in EGDT group, 4.0% patients in protocol-based standard therapy and in 3.6% patients in usual care group. Arterial lines for blood pressure monitoring were not required.

• Patients in the **usual care group** received the least amount of IVF during the first 6 hours (2.3 L in usual care vs 2.8 L in EGDT and 3.3 L in the protocol-based standard therapy group).

• Patients in the **EGDT group** received more dobutamine and PRBC during first 6 hours than protocol-based standard therapy and usual care. (dobutamine use, 8.0% vs. 1.1% and 0.9%, respectively; packed red-cell transfusions, 14.4% vs. 8.3% and 7

• Patients in both **protocol-based groups** received more **vasopressors** although use of antibiotics, glucocorticoids and activated protein C was same. All these differences disappeared between 6–72 hours..5%, respectively).
What they Found

- There were no differences observed in 60-day mortality (19-21%), 90-day mortality or 1-year mortality between groups.

- Protocol adherence was good (89.1% adherence in EGDT group and 95.6% adherence in protocol based standard therapy group).

- No differences were observed in secondary endpoints including cardiovascular failure, respiratory failure, hospital length of stay or discharge disposition;

- Incidence of acute renal failure was higher in protocol-based standard therapy (6% vs. 3% in the other groups).
What this means

- This study confirms the most important elements in management of sepsis

- **Early recognition, early administration of antibiotics, early adequate volume resuscitation** using clinical parameters and **avoiding over transfusion**.

- If these essential aspects of care are in place, protocolized measurements of central hemodynamics and oxygen saturation apparently do not improve patient outcomes measurably.