SEPSIS 2015

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DISCLOSURES

• William Johnson
  – No financial interests related to this presentation

FINANCIAL DISCLOSURES

• I do however have 3 children now going to college.
Surviving Sepsis Campaign
Guidelines for Management of Severe Sepsis and Septic Shock


Grading of Recommendations
Assessment, Development, and Evaluation (GRADE) Methodology

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (high)</td>
<td>RCTs</td>
</tr>
<tr>
<td>B (moderate)</td>
<td>Downgraded RCTs or upgraded observational studies</td>
</tr>
<tr>
<td>C (low)</td>
<td>Well-done observational studies with controls or downgraded RCTs</td>
</tr>
<tr>
<td>D (very low)</td>
<td>Downgraded controlled studies or expert opinions based on other evidence</td>
</tr>
</tbody>
</table>

SSC 2012 Guidelines
Initial Resuscitation
Hemodynamic Support

- Initial Resuscitation
- Fluid Therapy
- Vasopressor Therapy
- Inotropic Therapy
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 ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission.

Initial Resuscitation

- During the first 6 hours, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as a part of a treatment protocol (Grade 1C):
  - Central venous pressure 8-12 mm Hg
  - Mean arterial pressure ≥65 mm Hg
  - Urine output ≥0.5 mL/kg/h
  - Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively

Initial Resuscitation

- One randomized single-center trial demonstrated reduced mortality with early quantitative resuscitation for emergency department patients presenting with septic shock.
- Second multicenter randomized trial of 314 patients with severe sepsis in 8 Chinese centers reported a 17.7% absolute reduction in 28-day mortality (survival rates, 75.2% vs. 57.5%, P=0.001).
Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>EGDT</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital</td>
<td>46.5</td>
<td>30.5</td>
<td>0.58 (0.38-0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>28-day Mortality</td>
<td>49.2</td>
<td>33.3</td>
<td>0.58 (0.39 – 0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-day Mortality</td>
<td>56.9</td>
<td>44.3</td>
<td>0.67 (0.46-0.96)</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Initial Resuscitation

- 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)

- One multicenter randomized trial demonstrated that early quantitative resuscitation based on lactate clearance (decrease by at least 10%) was non-inferior to resuscitation based on achieving ScvO$_2$ of 70% or more.
  
  Jones A. JAMA. 2010;303:739–746.

- A second multicenter randomized trial demonstrated that a strategy based on >20% decrease in lactate levels per 2 hours of the first 8 hours, in addition to achievement of an ScvO$_2$ target, was associated with a 9.6% absolute reduction in mortality.
  
Early Lactate-Guided Therapy in Intensive Care Unit Patients

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 hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock. *(Grade 1B)*

Fluid Therapy - Mortality

- Three multicenter randomized trials showed no significant difference in mortality between crystalloids and hydroxyethyl starches.

- One multicenter randomized trial demonstrated increased mortality rates with HES 130/0.42 fluid resuscitation compared to Ringer acetate (51% vs 43%. *P*=0.03).
Fluid Therapy - Kidney injury

• Three multicenter randomized trials showed a significant increase in the risk of acute kidney injury with hydroxyethyl starch as compared with crystalloids.

• One multicenter randomized trial did not find an increase in the risk of acute kidney injury with hydroxyethyl starch as compared with crystalloids.

Fluid Therapy

• We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require repeated boluses of crystalloids. (Grade 2C)

Meta-analysis: Albumin versus Other Fluids

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative risk</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term mortality</td>
<td>242 per 1000</td>
<td>257 per 1000</td>
<td>0.64 (0.57 to 0.73)</td>
<td>281 (7 studies)</td>
<td>moderate</td>
</tr>
<tr>
<td>Short-term mortality</td>
<td>444 per 1000</td>
<td>257 per 1000</td>
<td>0.65 (0.57 to 0.73)</td>
<td>1402 (4 studies)</td>
<td>moderate</td>
</tr>
<tr>
<td>Short-term mortality</td>
<td>242 per 1000</td>
<td>195 per 1000</td>
<td>0.61 (0.53 to 0.7)</td>
<td>680 (20 studies)</td>
<td>moderate</td>
</tr>
</tbody>
</table>
Fluid Therapy
- 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)

Vasopressor Therapy
- 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)

Meta-analysis of Norepinephrine versus Dopamine

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
<th>Relative effect</th>
<th>Quality of the evidence</th>
<th>No. of participants (studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term mortality</td>
<td>Dopamine 330 per 1000</td>
<td>Norepinephrine 462 per 1000</td>
<td>RR 0.91 (0.82 to 0.99)</td>
<td>Moderate</td>
<td>2043 (6 studies)</td>
</tr>
<tr>
<td>Serious adverse events - Supraventricular arrhythmias</td>
<td>Dopamine 229 per 1000</td>
<td>Norepinephrine 62 per 1000</td>
<td>RR 0.47 (0.38 to 0.58)</td>
<td>Moderate</td>
<td>1931 (2 studies)</td>
</tr>
<tr>
<td>Serious adverse events - Ventricular arrhythmias</td>
<td>Dopamine 30 per 1000</td>
<td>Norepinephrine 15 per 1000</td>
<td>RR 0.35 (0.19 to 0.64)</td>
<td>Moderate</td>
<td>1931 (2 studies)</td>
</tr>
</tbody>
</table>

*The assumed risk is the median control group risk across studies. The corresponding risk is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio
1 Strong heterogeneity in the results (I² = 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.
2 Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, NEJM 2010. We have lowered the quality of evidence one level for indirectness.
**Vasopressor Therapy**

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

### Meta-analysis of Norepinephrine versus Epinephrine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative effect (95% CI)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term mortality</strong></td>
<td>RR 0.96 (0.77 to 1.21)</td>
<td>⊕⊕⊕⊝ moderate*</td>
</tr>
<tr>
<td>Study population</td>
<td>Epinephrine: 540, Norepinephrine: 540 (4 studies)</td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events - supraventricular arrhythmias</strong></td>
<td>RR 1.75 (0.62 to 5.35)</td>
<td>⊕⊕⊝ low*</td>
</tr>
<tr>
<td>Study population</td>
<td>Epinephrine: 130, Norepinephrine: 78 (5 studies)</td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events - ventricular arrhythmias</strong></td>
<td>RR 0.64 (0.27 to 1.51)</td>
<td>⊕⊕⊝ low*</td>
</tr>
<tr>
<td>Study population</td>
<td>Epinephrine: 130, Norepinephrine: 86 (5 studies)</td>
<td></td>
</tr>
</tbody>
</table>

*Grade reduced for imprecision.
1. Outcomes reported only in one of four trials.

### Vasopressor Therapy

- 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).
Vasopressor Therapy

- We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of arrhythmias and/or low heart rate). (Grade 2C)
- Phenylephrine is not recommended except in circumstances where:
  a) norepinephrine is associated with serious arrhythmias
  b) cardiac output is known to be high and blood pressure persistently low, or
  c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target. (Grade 1C)

Vasopressor Therapy

- We recommend that low-dose dopamine not be used for renal protection. (Grade 1A)
- We recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available

Inotropic Therapy

- We recommend that a trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of:
  a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or
  b) 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)
Screening for Sepsis and Performance Improvement

- We 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).
- Performance improvement efforts in severe sepsis should be used to improve patient outcomes (Ungraded).

Diagnosis

- 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).
Diagnosis

- 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 (e.g., 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).

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.

**Remark:** 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.

### Summary: Early Antibiotics for Sepsis/Septic Shock Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Outcome</th>
<th>Limitation</th>
<th>Other Outcome</th>
<th>Early vs. Late</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar</td>
<td>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>Barochia</td>
<td>2010 (2)</td>
<td>Meta-analysis</td>
<td>n=654</td>
<td>Observational</td>
<td>before-after</td>
<td>n= 4 studies, homogeneous, ( I^2 = 0% )</td>
<td>OR 0.58 (0.33-0.85), ( P &lt; .0001 )</td>
</tr>
<tr>
<td>Ferrer</td>
<td>2009 (3)</td>
<td>Multicenter (n=2796)</td>
<td>ss/SS; survival-HD</td>
<td>Observational</td>
<td>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>
</tr>
<tr>
<td>Barie</td>
<td>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</td>
<td>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</td>
<td>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>HR0.54 (0.33-0.86), ( P = .01 )</td>
<td>Low</td>
</tr>
<tr>
<td>Gurnani</td>
<td>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</td>
<td>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</td>
<td>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</td>
<td>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</td>
<td>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 RF. Crit Care Med. 2013;41:580-637
Antimicrobial Therapy

- 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).

Antimicrobial Therapy

- 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).

Antimicrobial Therapy

- We suggest that the duration of therapy typically be 7 to 10 days if clinically indicated; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (Grade 2C).
Corticosteroids

- We suggest 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, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (Grade 2C).

Hydrocortisone in Septic Shock (CORTICUS) 28-day Mortality


Corticosteroids

- We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B).
Corticosteroids

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

Blood Product Administration

- Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, we recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL in adults (Grade 1B).

- We recommend not using erythropoietin as a specific treatment of anemia associated with severe sepsis (Grade 1B).
SSC 2012 Guidelines
Glucose Control

- Glucose Control
- Bicarbonate Therapy

Glucose Control

- We recommend a 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).

Glucose Control

- Large randomized single-center trial (predominantly cardiac surgical ICU) demonstrated reduced ICU mortality with intensive intravenous insulin targeting blood glucose to 80–110 mg/dL.
- Second randomized trial of intensive insulin therapy using this protocol enrolled medical ICU patients with anticipated ICU length of stay of >3 days; overall mortality was not reduced.

Intensive Insulin Therapy in Critically Ill Patients

But.....
Glucose Control

- Subsequent RCTs studied mixed populations of surgical and medical ICU patients and found that intensive insulin therapy did not significantly decrease mortality, whereas the NICE-SUGAR trial demonstrated an increased mortality.


VISEP Intensive Insulin Trial

Intensive vs. Conventional Glucose Control in Critically Ill Patients
Glucose Control

- As there is no evidence that targets between 140 and 180 mg/dL are different from targets of 110 to 140 mg/dL, the recommendations use an upper target blood glucose ≤180 mg/dL without a lower target other than hypoglycemia.
- Treatment should avoid hyperglycemia (>180 mg/dL), hypoglycemia, and wide swings in glucose levels.


Severe Hypoglycemia ≤40 mg/dL (2.2 mmol/L)

- 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).

Bicarbonate Therapy

Surviving Sepsis Campaign

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Setting Goals of Care

• We recommend that the goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (Grade 1B).

Setting Goals of Care

• The quality of supporting evidence and strength of the revised recommendations for setting goals of care makes this an important consideration in the care of the patient with severe sepsis.
• Although this recommendation is listed last in the guidelines, it is not meant to be a last consideration of care.

CASE PRESENTATION

• 36yo presented to ER 23 weeks pregnant with fever
• Found to have intra-uterine fetal demise
• Post-vaginal delivery, patient decompensated and became hypotensive
CASE PRESENTATION

• Intensivist Consult obtained by OB-GYN and patient transferred to ICU
• Initial lab:
  – ABG: pH 7.19, pCO2 31, pO2 234
  – Creatinine: 1.2
  – Lactate: 7.7
• Sepsis protocol started and central line placed

CASE PRESENTATION

• Progressive decline during subsequent 24 hrs.
• Blood cultures grew E. coli.
• Patient intubated and placed on ventilator
• Progressive rise in Creatinine to 2.4 in 12 hours and no urine output.
  – CVVHD started by noon (about 12 hours after transfer to ICU).

CASE PRESENTATION

• ABG at start of CVVHD
  – pH 7.24, pCO2 27, pO2 85
• Maximal pressor support given with norepinephrine, vasopressin, and epinephrine.
• Crystalloid and colloids given attempting to maintain CVP at least 12.
CASE PRESENTATION

• Death imminent at 2100
  – Hypotensive with BP 60 systolic despite pressors
  – No urine output and hemodynamics too unstable to continue CVVHD
  – Ability to ventilate significantly declined
    • pH 6.99, pCO2 57, pO2 75