Septic Shock Mortality

Definitions

**SIRS:** 2 or more of the following:

- Core $T \geq 38$ or $\leq 36$
- $HR \geq 90$
- $RR \geq 20$ or $PaCO2 \leq 32$
- $WBC \geq 12,000$ or $\leq 4,000$
Definitions

- **Sepsis**: SIRS + known or suspected infection
- **Severe sepsis**: Sepsis with hypoperfusion or organ dysfunction (see next slide)
- **Septic shock**: ongoing tissue hypoperfusion = hypotension despite adequate fluid resuscitation or lactate >= 4
Organ Dysfunction

- **CV:** SBP $\leq 90$ mmHg or MAP $\leq 70$ mmHg for at least 1 hour despite adequate volume resuscitation, or the use of vasopressors to achieve the same goals.
- **Renal:** Urine output $< 0.5$ mL/kg/h, or acute renal failure
- **Pulmonary:** PaO2/FiO2 $\leq 250$ if other organ dysfunction present or $\leq 200$ if the lung is the only dysfunctional organ.
- **Hepatic** dysfunction (e.g., hyperbilirubinemia, transaminitis)
- **CNS:** Acute alteration in mental status (e.g., delirium).
- **Hematologic:** Platelet count $< 80,000$/mm$^3$ or decreased by 50 percent over three days, or disseminated intravascular coagulation.
- **Metabolic:** $pH \leq 7.30$ or base deficit $> 5.0$ mmol/L and plasma lactate $> 1.5 \times$ upper limit of normal.
Pathophysiology

- **Hypovolemia** loss of cardiac filling
  - Capillary leak (absolute hypovolemia)
  - Venodilation (relative hypovolemia)

- **Cardiogenic** decrease in contractility

- **Obstructive** rise in PVR

- **Distributive** hypoperfusion despite nl / incr CO
  - Macrovascular (decreased splanchnic flow)
  - Microvascular (shunting)

- **Cytotoxic** cellular inability to utilize O2 despite adequate supply

Dellinger: Crit Care Med, Volume 31(3). March 2003.946-955
Multiorgan Dysfunction

- Host immunosuppression (anergy, lymphopenia, hypothermia)
- Apoptosis initiated by proinflammatory cytokines
- Tissue injury and multiorgan dysfunction
Sepsis Progression

- Early: systemic O2 supply / demand imbalance
  *Hypovolemia, myocardial depression, increased metabolic rate and vasoregulatory perfusion abnormalities.*

- **Global tissue hypoxia: delivery dependent**
  *Transition to severe disease. Elevated lactate, decreased ScvO2. Can occur with normal vital signs.*

- **Septic shock:**
  - Hypodynamic state of O2 delivery dependency *(high lactate and low ScvO2)*
  - Hyperdynamic *(O2 consumption is independent of O2 delivery; normal or increased lactate and high ScvO2)*

Otero, R et al EGDT in Severe Sepsis Revisited Chest 130(5) 1579-1595
Oxygen Content Equation

\[ \text{CaO}_2 = (\text{SaO}_2 \times \text{Hgb} \times 1.34) + 0.003(\text{PaO}_2) \]

- \( \text{CaO}_2 \) in ml/dl arterial blood
- \( \text{SaO}_2 \) expressed as decimal fraction
- \( \text{Hgb} \) in g/dl
- 1.34 = \( \text{O}_2 \)-binding capacity of Hgb (ml O2/g Hgb)
- 0.003 = solubility constant (0.003 ml O2/dl/mm Hg PaO2)
O2 delivery

- Arterial O2 delivery = C.O. x CaO2
- Venous O2 delivery = C.O. x CvO2

If C.O. = 5 L/min and CaO2 = 20 ml O2/dl
O2 delivery = 1000 ml/min
Oxygen uptake

\[ \text{O}2 \text{ uptake} = \text{art O}2 - \text{ven O}2 \text{ delivery} \]

\[ \text{VO}2 = \text{C.O.} \times (\text{CaO}2 - \text{CvO}2) \]

\[ \text{VO}2 = 5 \text{ L/min} \times (0.2 \text{ L O}2/\text{L} - 0.15 \text{ L O}2/\text{L}) = 5 \times 0.05 = 0.25 \text{ L} = 250 \text{ ml} \]

\[ \text{O}2\text{ER: VO}2 / \text{DO}2 \times 100\% \] (Normal 20 - 30%)
Figure 12.1. Normal arterial and venous oxygen values. A normal pulmonary venous admixture of 3.0% is schematically shown as a shunt between the pulmonary artery and pulmonary venous circulations. RA, right atrium; RV, right ventricle; PA, pulmonary arteries; PV, pulmonary veins; LA, left atrium; LV, left ventricle. Modified from Martin L. Pulmonary physiology in clinical practice. St. Louis: Mosby-Year Book, 1987.
Rivers. et al Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock.

SIRS criteria and systolic blood pressure \( \leq 90 \text{ mm Hg} \) or lactate \( \geq 4 \text{ mmol/liter} \)

Assessment and consent

Randomization

Standard therapy in emergency department (n=133)

Early goal-directed therapy (n=130)

CVP \( \geq 8–12 \text{ mm Hg} \)

MAP \( \geq 65 \text{ mm Hg} \)

Urine output \( \geq 0.5 \text{ ml/kg/hr} \)

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

Continuous ScvO\(_2\) monitoring and early goal-directed therapy for \( \geq 6 \text{ hr} \)

CVP \( \geq 8–12 \text{ mm Hg} \)

MAP \( \geq 65 \text{ mm Hg} \)

Urine output \( \geq 0.5 \text{ ml/kg/hr} \)

ScvO\(_2\) \( \geq 70\% \)

SaO\(_2\) \( \geq 93\% \)

Hematocrit \( \geq 30\% \)

Cardiac index

\( \text{VO}_2 \)
Table 4. Treatments Administered.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hours after the Start of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–6</td>
</tr>
<tr>
<td>Total fluids (ml)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3499±2438</td>
</tr>
<tr>
<td>EGDT</td>
<td>4981±2984</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Red-cell transfusion (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>18.5</td>
</tr>
<tr>
<td>EGDT</td>
<td>64.1</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any vasopressor (%)†</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>30.3</td>
</tr>
<tr>
<td>EGDT</td>
<td>27.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.62</td>
</tr>
<tr>
<td>Inotropic agent (dobutamine) (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>0.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>13.7</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>53.8</td>
</tr>
<tr>
<td>EGDT</td>
<td>53.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
</tr>
<tr>
<td>Pulmonary-artery catheterization (%)‡</td>
<td></td>
</tr>
<tr>
<td>Standard therapy</td>
<td>3.4</td>
</tr>
<tr>
<td>EGDT</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Because some patients received a specific treatment both during the period from 0 to 6 hours and during the period from 7 to 72 hours, the cumulative totals for those two periods do not necessarily equal the values for the period from 0 to 72 hours. EGDT denotes early goal-directed therapy.

†Administered vasopressors included norepinephrine, epinephrine, dopamine, and phenylephrine hydrochloride.

‡All pulmonary-artery catheters were inserted while patients were in the intensive care unit.
<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.
The Importance of Early Goal-Directed Therapy for Sepsis-induced Hypoperfusion


NNT to prevent 1 event (death) = 6 - 8

- Standard therapy
- EGDT

Mortality (%) vs.
- In-hospital mortality (all patients)
- 28-day mortality
- 60-day mortality

A clinician attacks the three heads of severe sepsis—
hypotension, hypoperfusion, and organ dysfunction.
Initial Resuscitation

- Protocolized resuscitation
- CVP 8 – 12
- MAP > 65
- UO > = 0.5 ml/kg/h
- ScvO2 >= 70% or SvO2 > = 65%
Fluid Therapy

- Crystalloids and colloids are equally effective
- Target CVP $\geq 8$ ($\geq 12$ if mech vent)
- Initial bolus: Crystalloids: $\sim 1000$ cc; Colloids 300 – 500 cc over 30 min; repeat based on response and tolerance
Fluid Therapy

- Reduce rate of fluids when CVP or PCWP increase without concurrent hemodynamic improvement
- Venodilation and capillary leak: need for continuing aggressive treatment with fluids
- I >> O is typical; can’t use to judge fluid resuscitation during the first 24h
Vasopressors

- Hypotensive pt: loss of autoregulation and dependence of perfusion on pressure
- May need to start before correction of hypovolemia
- Titration of norepinephrine to MAP 65 has been shown to preserve tissue perfusion
- Baseline BP should be considered
Vasopressors

- Initial pressor of choice: norepinephrine or dopamine
- Vasopressin 0.03 U/min may be added
- Epinephrine in cases of poor response to norepi or dopa
- Central and A-lines
ScvO2 or SvO2 below target

- Transfuse RBC to achieve Hct $\geq 30$
- Dobutamine up to 20 mcg/kg/min
CORTICUS Study

- 50 mg hydrocortisone q 6h x 5d with 6-day taper vs. placebo
- Primary outcome: death at 28 days in ACTH stimulation test nonresponders
- No mortality difference in responders or nonresponders
- Faster shock reversal in hydrocortisone group
Corticosteroids

- IV hydrocortisone: cases of septic shock when BP is poorly responsive to fluid resuscitation and vasopressors. Do not exceed 300 mg hydrocortisone / day
- No need in ACTH stimulation test
- Wean steroids when vasopressors are no longer required
Other Issues

- Diagnosis
- Antibiotics
- Source control
- Activated Protein C
Supportive Therapy

- Transfuse for Hgb < 7 once tissue hypoperfusion resolved
- Mechanical ventilation
- Glucose control
- Nutrition
- DVT and stress ulcer prophylaxis
Activated Protein C

- Approved for patients with severe sepsis and increased risk of death
- APACHE II \( \geq 25 \) or dysfunction of 2 or more organs: absolute decrease in mortality 13% \(^6\)
- Not effective in patients with low risk of death \(^7\)
Vasopressin

- Consider in patients with refractory shock despite fluid resuscitation and high-dose conventional vasopressors.
- Dose 0.01 – 0.03 u/min
- May decrease stroke volume
- Not the first choice
Vasopressin

- Low VP levels (3.1 pg/ml) were found in a study of 19 patients with vasodilatory septic shock as compared to patients with cardiogenic shock (22.7 pg/ml).
- VP 0.04 u/min increased measured VP level and improved BP.

Columbia University
Vasopressin

- Prospective study of 239 mixed critically ill SICU patients and 70 healthy volunteers
- Study pts had higher AVP than healthy controls
- No correlation between serum AVP level and the incidence of shock.
- 4/239 patients met criteria for absolute (<0.83 pg/ml) and 32 patients met criteria for a relative AVP deficiency (AVP < 10 and MAP < 70).
- 22% of septic shock patients had relative AVP deficiency

Jochberger, S et al Crit Care Med 2006; 34(2) 293
Vasopressin

- 10 pts with vasodilatory septic shock admitted to a trauma ICU
- Randomized to VP 0.04 u/min or placebo
- 2 patients in the placebo group died of refractory hypotension. All patients in the VP group survived and had other pressors withdrawn (maintained BP on VP only).

Allegheny General Hospital Pittsburg
Vasopressin

- Prospective, case-controlled study of 16 patients with septic shock who remained hypotensive despite pharmacologic doses of catecholamines.
- VP 0.04 u/min x 16h
- BP, SVR and UO increased. Lactate decreased. No side effects.

Vasopressin

48 patients with catecholamine –resistant vasodilatory shock randomized to NE or AVP 4 u/h + NE and followed for 48h.

AVP pts: significantly lower HR, NE requirements and incidence of new-onset tachyarrhythmias. MAP, CI, SV and LVSWI were higher in AVP group. GI perfusion was better (by gastric tonometry), but bilirubin was higher in the AVP group. Dunser Circulation 2003; 107: 2313 – 2319

30.2% incidence of ischemic skin ulcers

Dunser Crit Care Med 2003; 31: 1394 – 1398
Ventilation

- ALI / ARDS is common
- Lung protective ventilation decreases mortality (from 40 to 31% in ARDS Network Study)\textsuperscript{17}, lessens organ dysfunction and lowers levels of cytokines.
- TV 6 cc/kg IBW
  Men 50 + 0.91(H cm – 152.4)
  Women 45.5 + 0.91(H cm – 152.4)
- PEEP doesn’t improve mortality\textsuperscript{18}. 
Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.