Surviving Sepsis Campaign
Guidelines for Management of Severe Sepsis/Septic Shock
An Overview

The Pathophysiology of Sepsis / SIRS and MOF

Objectives

- The Definitions of Sepsis and the Sepsis Syndromes.
- The Factors that precipitate and perpetuate the Sepsis Cascade.
- The Pathogenesis of Multiple Organ Dysfunction in Sepsis.
- Treatment options in Sepsis

What is Sepsis?

Sepsis Criteria (SCCM, ESICM, ACCP, ATS, SIS, 2001):

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<td>Fever</td>
<td>Temperature &gt; 38°C or &lt; 36°C</td>
</tr>
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<td>Hypotension</td>
<td>Arterial systolic blood pressure &lt; 90 mm Hg or &gt; 40 mm Hg decrease from baseline</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Heart rate &gt; 90 beats/min</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Respiratory rate &gt; 20 breaths/min or increased work of breathing</td>
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<td>Serum lactic acid &gt; 4 mg/dL</td>
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...
Definitions (ACCP/SCCM, 1991)

- **Systemic Inflammatory Response Syndrome (SIRS):** The systemic inflammatory response to a variety of severe clinical insults (For example, infection).
- **Sepsis:** The systemic inflammatory response to infection.

SIRS is manifested by two or more of the following conditions:

- Temperature >38 degrees Celsius or <36 degrees Celsius.
- Heart rate >90 beats per minute.
- Respiratory rate >20 breaths per minute or PaCO2 <32mmHg.
- White blood cell count > 12,000/cu mm, <4,000/ cu mm, or >10% band forms.

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**Definitions (ACCP/SCCM):**

- **Infection:** A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
- **Bacteremia:** The presence of viable bacteria in the blood.

Relationship Between Sepsis and SIRS

Definitions (ACCP/SCCM)

- **Sepsis:**
  - Known or suspected infection, plus
  - ≥2 SIRS Criteria.
- **Severe Sepsis:**
  - Sepsis plus ≥1 organ dysfunction.
  - MODS.
  - Septic Shock.
Definitions (ACCP/SCCM):
• Septic Shock: Sepsis induced with hypotension despite adequate resuscitation along with the presence of perfusion abnormalities which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

Definitions (ACCP/SCCM):
• Multiple Organ Dysfunction Syndrome (MODS): The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

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Clinical Signs of Sepsis
• Fever.
• Leukocytosis.
• Tachypnea.
• Tachycardia.
• Reduced Vascular Tone.
• Organ Dysfunction.

Clinical Signs of Septic Shock
• Hemodynamic Alterations
  • Hyperdynamic State (“Warm Shock”)
    - Tachycardia.
    - Elevated or normal cardiac output.
    - Decreased systemic vascular resistance.
  • Hypodynamic State (“Cold Shock”)
    - Low cardiac output.

Clinical Signs of Septic Shock
• Myocardial Depression.
• Altered Vasculature.
• Altered Organ Perfusion.
• Imbalance of O2 delivery and Consumption.
• Metabolic (Lactic) Acidosis.
Levels of Clinical Infection

- **Level I** Locally Controlled.
- **Level II** Locally Controlled, Leukocytosis.
- **Level III** Systemic Hyperdynamic Response.
- **Level IV** Oxygen metabolism becomes uncoupled.
- **Level V** Shock, Organ Failure.

Stages In the Development of SIRS (Bone, 1996)

- **Stage 1.** In response to injury / infection, the local environment produces cytokines.
- **Stage 2.** Small amounts of cytokines are released into the circulation:
  - Recruitment of inflammatory cells.
  - Acute Phase Response.
  - Normally kept in check by endogenous anti-inflammatory mediators (IL-10, PGE2, Antibodies, Cytokine receptor antagonists).

Stages In the Development of SIRS

- **Stage 3.** Failure to control inflammatory cascade:
  - Loss of capillary integrity.
  - Stimulation of Nitric Oxide Production.
  - Maldistribution of microvascular blood flow.
  - Organ injury and dysfunction.

Why is Sepsis Important?

Severe Sepsis

- Major cause of morbidity and mortality worldwide.
  - Leading cause of death in noncoronary ICU.
  - 11th leading cause of death overall.
  - More than 750,000 cases of severe sepsis in US annually.
  - In the US, more than 500 patients die of severe sepsis daily.

Severe Sepsis is deadly

- Sands, et al
- Zeni, et al
- Angus, et al
Severe Sepsis is Common

Severe Sepsis is increasing in incidence

Severe Sepsis is a Significant Healthcare Burden

- Sepsis consumes significant healthcare resources.
- In a study of Patients who contract nosocomial infections, develop sepsis and survive:
  - ICU stay prolonged an additional 8 days.
  - Additional costs incurred were $40,890/patient.
- Estimated annual healthcare costs due to severe sepsis in U.S. exceed $16 billion.

Mediators of Septic Response

Pro-inflammatory Mediators
- Bacterial Endotoxin
- TNF-α
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Platelet Activating Factor (PAF)
- Interferon-Gamma
- Prostaglandins
- Leukotrienes
- Nitric Oxide

Anti-inflammatory Mediators
- Interleukin-10
- PGE2
- Protein C
- Interleukin-6
- Interleukin-4
- Interleukin-12
- Lipoxins
- GM-CSF
- TGF
- IL-1RA
Mechanisms of Sepsis - Induced Organ Injury and Organ Failure

Question: Why do Septic Patients Die?

• Answer: Organ Failure

Organ Failure and Mortality

• Knaus, et al. (1986):
  • Direct correlation between number of organ systems failed and mortality.
  • Mortality Data:

<table>
<thead>
<tr>
<th>#OSF</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
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<tr>
<td>1</td>
<td>22%</td>
<td>31%</td>
<td>34%</td>
<td>35%</td>
<td>40%</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>52%</td>
<td>67%</td>
<td>66%</td>
<td>62%</td>
<td>56%</td>
<td>64%</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>80%</td>
<td>95%</td>
<td>93%</td>
<td>96%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Pathophysiology of Sepsis-Induced Organ Injury

• Multiple Organ Dysfunction (MODS) and Multiple Organ Failure (MOF) result from diffuse cell injury / death resulting in compromised organ function.

  • Mechanisms of cell injury / death:
    • Cellular Necrosis (ischemic injury).
    • Apoptosis.
    • Leukocyte-mediated tissue injury.
    • Cytopathic Hypoxia

Pathophysiology of Sepsis-Induced Ischemic Organ Injury

• Cytokine production leads to massive production of endogenous vasodilators.

• Structural changes in the endothelium result in extravasation of intravascular fluid into interstitium and subsequent tissue edema.

• Plugging of select microvascular beds with neutrophils, fibrin aggregates, and microthrombi impair microvascular perfusion.

• Organ-specific vasoconstriction.
**Pathogenesis of Vasodilation in Sepsis**

- **Loss of Sympathetic Responsiveness:**
  - Down-regulation of adrenergic receptor number and sensitivity, possible altered signal transduction.
- **Vasodilatory Inflammatory Mediators.**
- **Endotoxin has direct vasodilatory effects.**
  - Increased Nitric Oxide Production.

**Vasodilatory Inflammatory Mediators**

- Vasoactive Intestinal Peptide
- Bradykinin
- Platelet Activating Factor
- Prostanoids
- Cytokines
- Leukotrienes
- Histamine
- NO

**Microvascular Plugging in Sepsis**

- Decreased red cell deformability in inflammatory states.
- Microvascular sequestration of activated leukocytes and platelets.
- Sepsis is a Procoagulant State.
  - The extrinsic pathway may be activated in sepsis by upregulation of Tissue Factor on monocytes or endothelial cells.
  - Fibrinolysis appears to be inhibited in sepsis by upregulation of Plasminogen Activator Inhibitor.
  - A variety of pathways result in reduced Protein C activity in sepsis.

**Endothelial Dysfunction in Sepsis**

- Endothelial cell expression of Selectins and ICAM / ELAM is upregulated in Sepsis due to inflammatory activation.
  - Selectins bind carbohydrate ligands on the surfaces of PMN’s.
  - ICAM bind Integrins on the surfaces of PMN’s.
  - The Selectins initiate a weak bond between the PMN and the endothelial cell causing PMN’s to tumble along the vessel wall.

**Pathogenesis of Endothelial Cell Dysfunction in Sepsis**

- Binding of leukocytes to ICAM leads to transmigration of PMN’s into interstitium.
- Transmigration disrupts normal cell-cell adhesions resulting in increased vascular permeability and tissue edema.
- Vascular permeability is also increased by several types of inflammatory cytokines.
Apoptosis in Sepsis
- A physiologic process of homeostatically-regulated programmed cell death to eliminate dysfunctional or excessive cells.
- A number of inflammatory cytokines, NO, low tissue perfusion, oxidative injury, LPS, and glucocorticoids all are known to increase apoptosis in endothelial and parenchymal cells.
- Levels of circulating sfas (circulating apoptotic receptor) and nuclear matrix protein (general cell death marker) are both elevated in MODS.

Leukocyte-Mediated Tissue Injury
- Transmigration and release of elastase and other degradative enzymes can disrupt normal cell-cell connections and normal tissue architecture required for organ function.
- Reactive oxygen species cause direct cellular DNA and membrane damage and induce apoptosis.

Cytopathic Hypoxia
- A defect of cellular oxygen utilization.
- May be due to activation of PARP (poly-ADP-ribosylpolymerase-1).
- Oxidative DNA damage activates PARP which consumes intracellular and mitochondrial NAD+.
- NAD+ depletion leads to impaired respiration and a shift to anaerobic metabolism.

Therapy For Sepsis

Therapeutic Strategies in Sepsis
- Optimize Organ Perfusion
  - Expand effective blood volume.
  - Hemodynamic monitoring.
  - Early goal-directed therapy.
    - 16% reduction in absolute risk of in-house mortality.
    - 39% reduction in relative risk of in-house mortality.
    - Decreased 28 day and 60 day mortality.
    - Less fluid volume, less blood transfusion, less vasopressor support, less hospital length of stay.

  - Pressors may be necessary.
    - Compensated Septic Shock:
      - Phenylephrine
      - Norepinephrine
      - Dopamine
      - Vasopressin
    - Uncompensated Septic Shock:
      - Epinephrine
      - Dobutamine + Phenylephrine / Norepinephrine
### Therapeutic Strategies in Sepsis

- **Control Infection Source**
  - Drainage
    - Surgical
    - Radiologically-guided
  - Culture-directed antimicrobial therapy
  - Support of reticuloendothelial system
    - Enteral / parenteral nutritional support
    - Minimize immunosuppressive therapies

- **Support Dysfunctional Organ Systems**
  - Renal replacement therapies (CVVHD, HD).
  - Cardiovascular support (pressors, inotropes).
  - Mechanical ventilation.
  - Transfusion for hematologic dysfunction.
  - Minimize exposure to hepatotoxic and nephrotoxic therapies.

### Experimental Therapies in Sepsis

- **Modulation of Host Response**
  - Targeting Endotoxin
    - Anti-endotoxin monoclonal antibody failed to reduce mortality in gram negative sepsis.
  - Neutralizing TNF
    - Excellent animal data.
    - Large clinical trials of anti-TNF monoclonal antibodies showed a very small reduction in mortality (3.5%).

- **IL-1 Antagonism**
  - Three randomized trials: Only 5% mortality improvement.

- **PAF-degrading enzyme**
  - Great phase II trial.
  - Phase III trial stopped due to no demonstrable efficacy.

- **NO Antagonist (LNMA)**
  - Increased mortality (P Pulmonary Hypertension).

- **Antithrombin III**
  - No therapeutic effect.
  - Subset of patients with effect when concomitant heparin not given.

- **Activated Protein C (Drotrecogin alpha / Xigris)**
  - Statistically significant 6% reduction in mortality.
  - Well-conducted multicenter trial (PROWESS).
  - FDA-approved for use in reduction of mortality in severe sepsis (sepsis with organ failure).

- **Activated Protein C (Drotrecogin alpha / Xigris)**
  - PROWESS Study
    - #MOD Mortality Reduction
      | #MOD | Absolute | Relative |
      |------|---------|---------|
      | ≥4   | 11%     | 22%     |
      | 3    | 8%      | 24%     |
      | 2    | 5%      | 20%     |
      | 1    | 2%      | 8%      |

### Mediator-Directed Therapies

- **Coagulation System**
  - **Xigris (Drotrecogin alpha/activated Protein C)**
    - PROWESS Study
Experimental Therapies in Sepsis
• Modulation of Host Response
  - Corticosteroids
    • Multiple studies from 1960’s – 1980’s: Not helpful, possibly harmful.

Evidence-Based Sepsis Guidelines
• Incorporation of data from the existing medical literature in the design of guidelines for the care of patients with severe sepsis and septic shock.
  • Guideline development strongly advocated by multiple critical care societies.
  • Guideline development for the reduction of mortality in sepsis is part of the 100K lives Campaign of IHI and is likely to soon become a JCAHCO requirement.

Evidence-Based Sepsis Guidelines
• Components:
  - Early Recognition
  - Early Goal-Directed Therapy
  - Monitoring
  - Resuscitation
  - Pressor / Inotropic Support
  - Steroid Replacement
  - Recombinant Activated Protein C
  - Source Control
  - Glycemic Control
  - Nutritional Support
  - Adjuncts: Stress Ulcer Prophylaxis, DVT Prophylaxis, Transfusion, Sedation, Analgesia, Organ Replacement

Evidence-Based Sepsis Guidelines

Surviving Sepsis
A global program to:
Reduce mortality rates in severe sepsis
Surviving Sepsis

Phase 1  Barcelona declaration
Phase 2  Evidence based guidelines
Phase 3  Implementation and education

Sponsoring Organizations

- American Association of Critical Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- Australasian and New Zealand Intensive Care Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Respiratory Society
- International Sepsis Forum
- Society of Critical Care Medicine
- Surgical Infection Society

Guidelines Committee*

Dellinger (RP)
Carlet
Masur
Gerlach
Levy
Vincent
Calandra
Colice
Gea-Banacloche
Keh
Marshall
Parker

Ramsay
Zimmerman
Bonten
Brun-Buisson
Caricillo
Cordonnier
Dellinger (EP)
Dhainaut
Finch
Finfer
Fourrier

Harvey
Hazelzet
Holtenberg
Jorgensen
Maier
Maki
Marini
Ospal
Osborn
Parrillo
Rhodes
Sevransky

Sprung
Torres
Vender
Bennet
Bochud
Cariou
Murphy
Mitsu
Szokel
Trzeciak
Visonneau

*Primary investigators from recently performed positive trials with implications for septic patients excluded from committee selection.

Surviving Sepsis Campaign (SSC)
Guidelines for Management of Severe Sepsis and Septic Shock


Crit Care Med 2004;32:858-873
Intensive Care Med 2004;30:536-555
available online at www.springerlink.com
www.sccm.org
www.sepsisforum.com
Crit Care Med 2008;36:296-327

Sackett DL. Chest 1989; 95:2S–4S
Sprung CL, Bernard GR, Dellinger RP. Intensive Care Medicine 2001; 27(Suppl):S1-S2
Clarifications

- Recommendations grouped by category and not by hierarchy
- Grading of recommendation implies literature support and not priority of importance

Initial Resuscitation

- In the presence of sepsis-induced hypoperfusion
  - Hypotension
  - Lactic acidosis

The Importance of Early Goal-Directed Therapy for Sepsis Induced Hypoperfusion

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

Initial Resuscitation

Goals during first 6 hours:

- Central venous pressure: 8–12 mm Hg
- Mean arterial pressure ≥ 65 mm Hg
- Urine output ≥ 0.5 mL kg\(^{-1}\) hr\(^{-1}\)
- Central venous (superior vena cava) or mixed venous oxygen \([\text{SvO}_2]\) saturation ≥ 70%  
  \[\text{Central venous} \geq 70\% \text{ or Mixed venous} \geq 65\%\]  
  \[\text{Grade B}\]

Initial Resuscitation

Goals during first 6 hours:

- Central venous or mixed venous \(\text{O}_2\) sat < 70% after CVP of 8–12 mm Hg
  - Packed RBCs to Hct 30%
  - Dobutamine to max 20 \(\mu\)g/kg/min
  \[\text{Grade B}\]

Diagnosis

- Appropriate cultures
- Minimum 2 blood cultures
  - 1 percutaneous
  - 1 from each vascular access ≥ 48 hrs
  - Culture other sites as clinically indicated
  \[\text{Grade D}\]

Antibiotic Therapy

- Begin intravenous antibiotics within first hour of recognition of severe sepsis. and in septic shock.  
  As early as possible  
  \[\text{Grade E}\]

Antibiotic Therapy

- One or more drugs active against likely bacterial or fungal pathogens.  
  Broad-spectrum
- Consider microorganism susceptibility patterns in the community and hospital.
  \[\text{Grade D}\]

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<table>
<thead>
<tr>
<th>MAP</th>
<th>65 mm Hg</th>
<th>75 mm Hg</th>
<th>85 mm Hg</th>
<th>F/L T</th>
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<tbody>
<tr>
<td>Urinary output (mL)</td>
<td>49 ±18</td>
<td>56 ± 21</td>
<td>43 ±13</td>
<td>.60/.71</td>
</tr>
<tr>
<td>Capillary blood flow (mL/min/100 g)</td>
<td>6.0 ± 1.6</td>
<td>5.9 ± 11</td>
<td>5.3 ± 0.9</td>
<td>.59/.55</td>
</tr>
<tr>
<td>Red Cell Velocity (au)</td>
<td>0.42 ± 0.06</td>
<td>0.44 ±0.16</td>
<td>0.42±0.06</td>
<td>.74/.97</td>
</tr>
<tr>
<td>Pico₂ (mm Hg)</td>
<td>41 ± 2</td>
<td>47 ± 2</td>
<td>46 ± 2</td>
<td>.11/.12</td>
</tr>
<tr>
<td>Pa-Pico₂ (mm Hg)</td>
<td>13 ± 3</td>
<td>17 ± 3</td>
<td>16 ± 3</td>
<td>.27/.40</td>
</tr>
</tbody>
</table>

Adapted from Table 4, page 2731, with permission from LeDoux, Astiz ME, Carpati CM, Rackow E. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000; 28:2729-2732.
Antibiotic Therapy

Reassess antimicrobial regimen at 48-72 hrs

- Microbiologic and clinical data
- Narrow-spectrum antibiotics
- Non-infectious cause identified
- Prevent resistance, reduce toxicity, reduce costs

Pseudomonas
Combined therapy in neutropenic patients
Duration typically limited to 7-10 days

Grade E

Source Control

- Evaluate patient for a focused infection amenable to source control measures including abscess drainage or tissue debridement.
  - Move rapidly
  - Consider physiologic upset of measure
  - Intravascular access devices

Grade E

Fluid Therapy

- Fluid resuscitation may consist of natural or artificial colloids or crystalloids.

Grade C
Fluid Therapy

- Fluid challenge over 30 min
  - 500–1000 ml crystalloid
  - 300–500 ml colloid
- Repeat based on response and tolerance

> Target a CVP > 8 mmHg (> 12 mmHg if MV)
> Use a fluid challenge technique
> Reduce rate if cardiac filling pressures increase without concurrent hemodynamic improvement

Grade E

Vasopressors

- Either norepinephrine or dopamine administered through a central catheter is the initial vasopressor of choice.
  - Failure of fluid resuscitation
  - During fluid resuscitation
- Avoid epinephrine, phenylephrine or vasopressin as the initial vasopressors of choice
- Use epinephrine as the first alternative when poorly responsive to norepinephrine

Grade D

Vasopressors

- Do not use low-dose dopamine for renal protection.

Grade B


Vasopressors

- In patients requiring vasopressors, place an arterial catheter as soon as possible.

Grade E
Circulating Vasopressin Levels in Septic Shock


Vasopressin and Septic Shock

- Versus cardiogenic shock
- Decreases or eliminates requirements of traditional pressors
- As a pure vasopressor expected to decrease cardiac output

Vasopressors

- Not a replacement for norepinephrine or dopamine as a first-line agent
- Consider in refractory shock despite high-dose conventional vasopressors
- If used, administer at 0.01-0.04 units/minute in adults
  
  0.03 units/minute

Grade E

During Septic Shock

Images used with permission from Joseph E. Parrillo, MD

Inotropic Therapy

- Consider dobutamine in patients with measured low cardiac output despite fluid resuscitation.
- Continue to titrate vasopressor to mean arterial pressure of 65 mm Hg or greater.

Grade E

Inotropic Therapy

- Do not increase cardiac index to achieve an arbitrarily predefined elevated level of oxygen delivery.

Grade A

Gattinoni, et al. NEJM 1995; 333:1025-1032
Steroid Therapy

> Annane, Bollaert and Briegel
> - Different doses, routes of administration and stopping/tapering rules

> Annane
> - Required hypotension despite therapeutic intervention

> Bollaert and Briegel
> - Required vasopressor support only

Identification of Relative Adrenal Insufficiency

Recommendations vary based on different measurements and different cut-off levels
- Peak cortisol after stimulation
- Random cortisol
- Incremental increase after stimulation
- Lower dose ACTH stimulation test
- Combinations of these criteria

Steroids

> Treat patients who still require vasopressors despite fluid replacement with hydrocortisone 200-300 mg/day, for 7 days in three or four divided doses or by continuous infusion.

Grade C
Steroids

Optional:
- Adrenocorticotropic hormone (ACTH) stimulation test (250-µg)

Continue treatments only in nonresponders (rise in cortisol ≤9 µg/dl)

Grade E

Dexamethasone and Cortisol Assay

Steroids

Optional:
- Decrease steroid dose if septic shock resolves.

Grade E

Steroids

Optional:
- Taper corticosteroid dose at end of therapy.

Grade E

Immunologic and Hemodynamic Effects of “Low-Dose” Hydrocortisone in Septic Shock

Figure 3, page 515, reproduced with permission from Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of “low dose” hydrocortisone in septic shock. Am J Respir Crit Care Med 2003; 167:512-520

Steroids

Optional:
- Add fludrocortisone (50 µg orally once a day) to this regimen.

Grade E
19

ADRENALS AND SURVIVAL FROM ENDOTOXEMIA

INTACT
SHAM
ADRX
MEDX

DEATH %

0
10
20
30
40
50
60
70
80
90

Steroids

Do not use corticosteroids >300 mg/day of hydrocortisone to treat septic shock.

Grade A

Adapted from Figure 7, page 437, with permission from Witek-Janusek L, Yelich MR. Role of the adrenal cortex and medulla in the young rats’ glucoregulatory response to endotoxin. Shock 1999; 3:434-439

Steroids

Do not use corticosteroids >300 mg/day of hydrocortisone to treat septic shock.

Grade A

Adapted from Figure 7, page 437, with permission from Witek-Janusek L, Yelich MR. Role of the adrenal cortex and medulla in the young rats’ glucoregulatory response to endotoxin. Shock 1999; 3:434-439

Results: 28-Day All-Cause Mortality

Primary analysis results

2-sided p-value 0.005
Adjusted relative risk reduction 19.4%
Increase in odds of survival 38.1%

30.8%
24.7%

Mortality (%)

Placebo
(n=840)

Drotrecogin
alfa
(activated)
(n=850)

6.1% absolute reduction in mortality


Mortality and APACHE II Quartile

APACHE II Quartile

1st (3-19) 2nd (20-24) 3rd (25-29) 4th (30-53)

Placebo

Drotrecogin
alfa
(activated)

118.8%

*Numbers above bars indicate total deaths

Adapted from Figure 2, page S90, with permission from Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. Crit Care Med 2003; 31[Suppl.]:S85-S90

Patient Selection for rhAPC

- Full support patient
- Infection induced organ/system dysfunction
- High risk of death
- No absolute contraindications


Human Activated Protein C Endogenous Regulator of Coagulation

Protein C (Inactive)

Protein C Activity

Blood Vessel Blood Flow

Thrombin

Protein C Receptor

Thrombomodulin
Mortality and Numbers of Organs Failing

![Mortality and Numbers of Organs Failing](image)

Adapted from Figure 4, page S91, with permission from Bernard GR. Drotrecogin alfa (activated) (recombinant human activated protein C) for the treatment of severe sepsis. *Crit Care Med* 2003;31[Suppl.]:S85-S90

Recombinant Human Activated Protein C (rhAPC)

- High risk of death
  - APACHE II ≥ 25
  - Sepsis-induced multiple organ failure
  - Septic shock
  - Sepsis-induced ARDS
- No absolute contraindications
- Weigh relative contraindications

Grade B

Surviving Sepsis Campaign 2008

![Surviving Sepsis Campaign 2008](image)


Transfusion Strategy in the Critically Ill

![Transfusion Strategy in the Critically Ill](image)

Blood Product Administration

- Red Blood Cells
  - Tissue hypoperfusion resolved
  - No extenuating circumstances
    - Coronary artery disease
    - Acute hemorrhage
    - Lactic acidosis
  - Transfuse < 7.0 g/dl to maintain 7.0-9.0 g/dL

Grade B

Blood Product Administration

- Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons.

Grade B
Blood Product Administration

Fresh frozen plasma
- Bleeding
- Planned invasive procedures.

Grade E

Blood Product Administration

- Do not use antithrombin therapy.

Grade B

Warren et al. JAMA. 2001; 1665-1678

Blood Product Administration

- Platelet administration
  - Transfuse for < 5000/mm³
  - Transfuse for 5000/mm³ – 30,000/mm³ with significant bleeding risk
  - Transfuse < 50,000/mm³ for invasive procedures or bleeding

Grade E

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

ARDSnet Mechanical Ventilation Protocol

Results: Mortality

Adapted from Figure 1, page 1306, with permission from The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342:1301-1312
Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- Reduce tidal volume over 1–2 hrs to 6 ml/kg predicted body weight
- Maintain inspiratory plateau pressure < 30 cm H₂O

Grade B

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- Minimum PEEP
  - Prevent end expiratory lung collapse
- Setting PEEP
  - FIO₂ requirement
  - Thoracopulmonary compliance

Grade E

The Role of Prone Positioning in ARDS

- 70% of prone patients improved oxygenation
- 70% of response within 1 hour
- 10-day mortality rate in quartile with lowest PaO₂:FIO₂ ratio (c88)
  - Prone: 23.1%
  - Supine: 47.2%

Kaplan-Meier estimates of survival at 6 months


The Role of Prone Positioning in ARDS

- Consider prone positioning in ARDS when:
  - Potentially injurious levels of F₁O₂ or plateau pressure exist
  - Not at high risk from positional changes

Grade E

Mechanical Ventilation of Severe Sepsis

- Semirecumbent position unless contraindicated with head of the bed raised to 45°

Grade C

Drakulovic et al. Lancet 1999; 354:1851-1855

Mechanical Ventilation of Septic Patients

- Use weaning protocol and a spontaneous breathing trial (SBT), at least daily

Grade A

Esteban, et al. AJRCCM 1997; 155:455-465
Esteban, et al. AJRCCM 1999; 159:512-518
Mechanical Ventilation of Septic Patients

SBT options
- Low level of pressure support with continuous positive airway pressure 5 cm H₂O
- T-piece

Prior to SBT
- Arousalable
- Hemodynamically stable (without vasopressor agents)
- No new potentially serious conditions
- Low ventilatory and end-expiratory pressure requirements
- Requiring levels of FIO₂ that could be safely delivered with a face mask or nasal cannula

Sedation and Analgesia in Sepsis

- Sedation protocol for mechanically ventilated patients with standardized subjective sedation scale target.
  - Intermittent bolus
  - Continuous infusion with daily awakening/retitration

Neuromuscular Blockers

- Avoid if possible
- Used longer than 2-3 hrs
  - PRN bolus
  - Continuous infusion with twitch monitor

Glucose Control

- After initial stabilization
  - Glucose < 150 mg/dL
  - Continuous infusion insulin and glucose or feeding (enteral preferred)
  - Monitoring
    - Initially q30–60 mins
    - After stabilization q4h

Glucose Control

Renal Replacement

- Absence of hemodynamic instability
  - Intermittent hemodialysis and continuous venovenous filtration equal (CVVH)
- Hemodynamic instability
  - CVVH preferred

Grade B

Bicarbonate Therapy

- Bicarbonate therapy not recommended to improve hemodynamics in patients with lactate induced pH >7.15

Grade C

Mathieu, et al. CCM 1991; 19:1352-1356

Bicarbonate Therapy

Changing pH Has Limited Value

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>NaHCO3 (2 mEq/kg)</td>
<td>pH 7.22</td>
<td>7.36</td>
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<tr>
<td></td>
<td>PAOP 15</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Cardiac output 6.7</td>
<td>7.5</td>
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<tr>
<td>0.9% NaCl</td>
<td>pH 7.24</td>
<td>7.23</td>
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<tr>
<td></td>
<td>PAOP 14</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Cardiac output 6.6</td>
<td>7.3</td>
</tr>
</tbody>
</table>


Deep Vein Thrombosis Prophylaxis

- Heparin (UH or LMWH)
- Contraindication for heparin
  - Mechanical device (unless contraindicated)
- High risk patients
  - Combination pharmacologic and mechanical

Grade A

Primary Stress Ulcer Risk Factors Frequently Present in Severe Sepsis

- Mechanical ventilation
- Coagulopathy
- Hypotension

Choice of Agents for Stress Ulcer Prophylaxis

- H$_2$ receptor blockers
- Role of proton pump inhibitors

Grade C

Consideration for Limitation of Support

- Advance care planning, including the communication of likely outcomes and realistic goals of treatment, should be discussed with patients and families. Decisions for less aggressive support or withdrawal of support may be in the patient’s best interest.

Surviving Sepsis

Phase 1 Barcelona declaration
Phase 2 Evidence based guidelines Paediatric issues
Phase 3 Implementation and education

Fluid Resuscitation

- Aggressive fluid resuscitation with boluses of 20 ml/kg over 5-10 min
- Blood pressure by itself is not a reliable endpoint for resuscitation
- Initial resuscitation usually requires 40-60 ml/kg, but more may be required

Hemodynamic Support

- Hemodynamic profile may be variable
- Dopamine for hypotension
- Epinephrine or norepinephrine for dopamine-refractory shock
- Dobutamine for low cardiac output state
- Inhaled NO useful in neonates with post-partum pulmonary hypertension and sepsis

Therapeutic Endpoints

- Capillary refill < 2 sec
- Warm extremities
- Urine output > 1 ml/kg/hr
- Normal mental status
- Decreased lactate
- Central venous O₂ saturation > 70%

Other Therapies

- Steroids: recommended for children with catecholamine resistance and suspected or proven adrenal insufficiency.
- Activated protein C not studied adequately in children yet.
- GM-CSF shown to be of benefit in neonates with sepsis and neutropenia.
- Extracorporeal membrane oxygenation (ECMO) may be considered in children with refractory shock or respiratory failure.
Sepsis Resuscitation Bundle
- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions

In the event of hypotension and/or lactate >4 mmol/L (36 mg/dl):
- Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent*)
- Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mm Hg

*See the individual chart measurement tool for an equivalency chart.

Sepsis Management Bundle
- Low-dose steroids* administered for septic shock in accordance with a standardized ICU policy
- Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy

Glucose control maintained ≥ lower limit of normal, but < 150 mg/dl (8.3 mmol/L)
- Inspiratory plateau pressures maintained < 30 cm H₂O for mechanically ventilated patients.

*See the individual chart measurement tool for an equivalency chart.
Sepsis Resuscitation Bundle

- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dl):
  - Achieve central venous pressure (CVP) of 8 mm Hg
  - Achieve central venous oxygen saturation (ScvO₂) of ≥ 70%**

**Achieving a mixed venous oxygen saturation (SvO₂) of 65% is an acceptable alternative.

A clinician, armed with the sepsis bundles, attacks the three heads of severe sepsis: hypotension, hypoperfusion and organ dysfunction. Crit Care Med 2004; 320(Suppl):S595-S597


www.survivingsepsis.org

Acknowledgment

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