Surviving Sepsis Campaign

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):

Table 1 Diagnostic criteria for sepsis

Infection[a]	
Documented or suspected *and* some of the following[b]:	
General parameters	
Fever (core temperature >38.3°C)	
Hypothermia (core temperature <36°C	
Heart rate >90 bpm or >2 SD above the normal value for age	
Tachypnea: >30 bpm	
Altered mental status	
Significant edema or positive fluid balance (>20 ml/kg over 24 h)	
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes	
Inflammatory parameters	
Leukocytosis (white blood cell count >12,000/μl)	
Leukopenia (white blood cell count <4,000/μl)	
Normal white blood cell count with >10% immature forms	
Plasma C reactive protein >2 SD above the normal value	
Plasma procalcitonin >2 SD above the normal value	
Hemodynamic parameters	
Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)	
Mixed venous oxygen saturation >70%[b]	
Cardiac index >3.5 l min^{-1} m^{-2}[b]	
Organ dysfunction parameters	
Arterial hypoxemia ($PaO_2/FIO2$ <300)	
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)	
Creatinine increase ≥0.5 mg/dl	
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)	
Ileus (absent bowel sounds)	
Thrombocytopenia (platelet count <100,000/μl)	
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)	
Tissue perfusion parameters	
Hyperlactatemia (>3 mmol/l)	
Decreased capillary refill or mottling	

[a] Defined as a pathological process induced by a micro-organism

[b] Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

[c] Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

[d] Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ functions: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

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

Table 2 The PIRO system for staging sepsis

Domain	Present	Future	Rationale
Predisposition	Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, gender	Genetic polymorphisms as components of inflammatory response (e.g., Toll-like receptor, tumor necrosis factor, interleukin 1, CD14); enhanced understanding of specific interactions between pathogens and host diseases	At the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult depend heavily on genetic predisposition (future)
Insult (infection)	Culture and sensitivity of infecting pathogen; detection of disease amenable to source control	Assay of microbial products (lipopolysaccharide, exotoxin, bacterial DNA); gene transcript profiles	Specific therapies directed against inciting insult require demonstration and characterization of that insult
Response	SIRS, other signs of sepsis, shock, C-reactive protein	Nonspecific markers of activated inflammation (e.g., procalcitonin or interleukin 6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, tumor necrosis factor, platelet-activating factor)	Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator
Organ dysfunction	Organ dysfunction as number of failing organs or composite score (e.g., multiple-organ dysfunction syndrome, logistic organ dysfunction system, Sequential Organ Failure Assessment, Pediatric Multiple Organ Dysfunction, Pediatric Logistic Organ Dysfunction)	Dynamic measures of cellular response to insult – apoptosis, cytopathic hypoxia, cell stress	Response to preemptive therapy (e.g., targeting micro-organism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present

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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Scheme 1. Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:

General variables
- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min^{-1} or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12,000 µL^{-1})
- Leukopenia (WBC count <4000 µL^{-1})
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic variables
- Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)

Organ dysfunction variables
- Arterial hypoxemia (Pa_{O_2}/Fi_{O^2} <300)
- Acute oliguria (urine output <0.5 mL/Kg hr or 45 mmol/L for at least 2 hrs, despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 µmol/L
- Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count, <100,000 µL^{-1})
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 µmol/L)

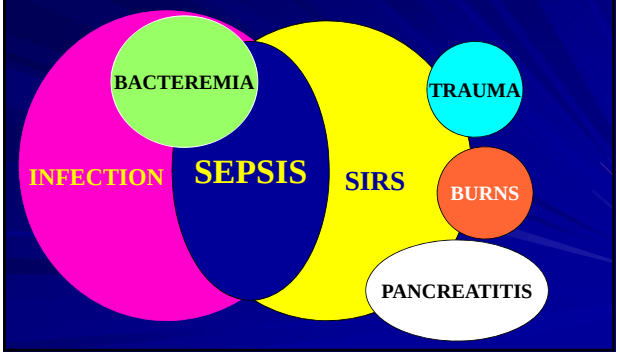
Tissue perfusion variables
- Hyperlactatemia (> upper limit of lab normal)
- Decreased capillary refill or mottling

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

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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Severe sepsis = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

Sepsis-induced hypotension
Lactate greater than the upper limits of normal laboratory results
Urine output <0.5 mL/kg hr for >2 hrs, despite adequate fluid resuscitation
ALI with Pao_2/Fio_2 <250 in the absence of pneumonia as infection source
ALI with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 µmol/L)
Bilirubin >2 mg/dL (34.2 µmol/L)
Platelet count <100,000
Coagulopathy (INR >1.5)

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

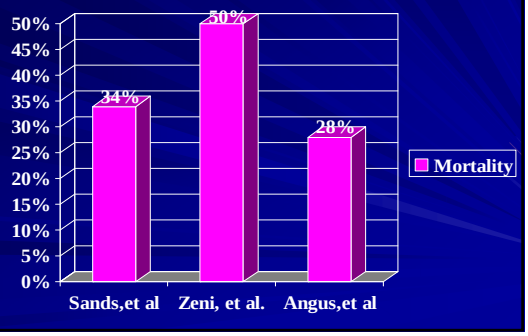
- **Stage 3.** Failure to control inflammatory cascade:
  - Loss of capillary integrity.
  - Stimulation of Nitric Oxide Production.
  - Maldistribution of microvascular blood flow.
  - Organ injury and dysfunction.

Why is Sepsis Important?

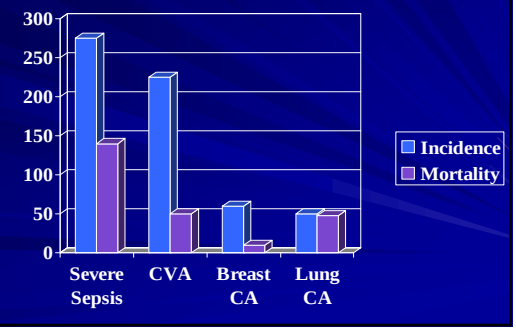
Severe Sepsis

- 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.

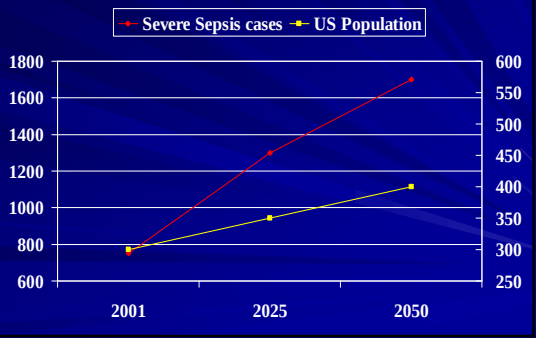
Severe Sepsis is deadly



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:

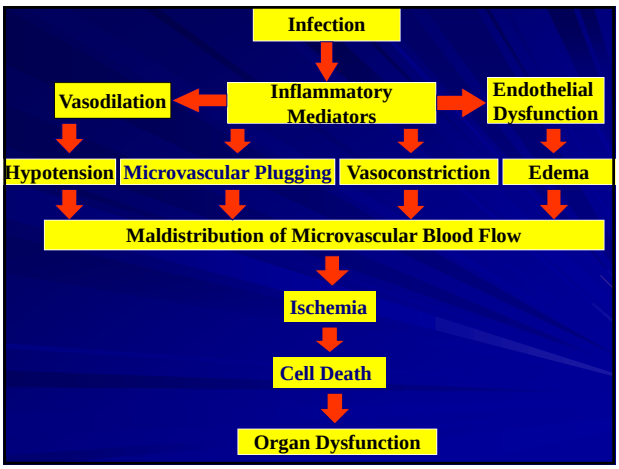
#OSF	D1	D2	D3	D4	D5	D6	D7
1	22%	31%	34%	35%	40%	42%	41%
2	52%	67%	66%	62%	56%	64%	68%
3	80%	95%	93%	96%	100%	100%	100%

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.

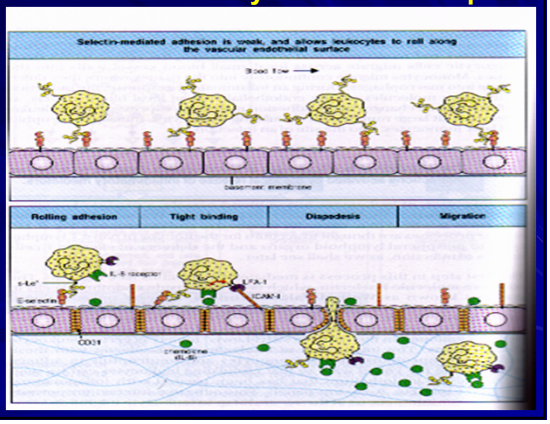
Endothelial Dysfunction in Sepsis

- 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.

Endothelial Cell Dysfunction in Sepsis



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.

Therapeutic Strategies in Sepsis

- Optimize Organ Perfusion
  - 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

Therapeutic Strategies in Sepsis

- 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%).

Experimental Therapies in Sepsis

- Modulation of Host Response
  - 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 (? Pulmonary Hypertension).

Experimental Therapies in Sepsis

- Modulation of Host Response
  - 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).

Mediator-Directed Therapies

- Coagulation System
  - Xigris (Drotrecogin alpha/activated Protein C
    - PROWESS Study

#MOD	Mortality Reduction	
	Absolute	*Relative*
≥4	11%	22%
3	8%	24%
2	5%	20%
1	2%	8%

Experimental Therapies in Sepsis

- Modulation of Host Response
  - Corticosteroids
    - Multiple studies from 1960's – 1980's: Not helpful, possibly harmful.
    - Annane, et al. (2002): 10% mortality reduction in vasopressor-dependent septic shock (relative adrenal insufficiency, ACTH nonresponders).

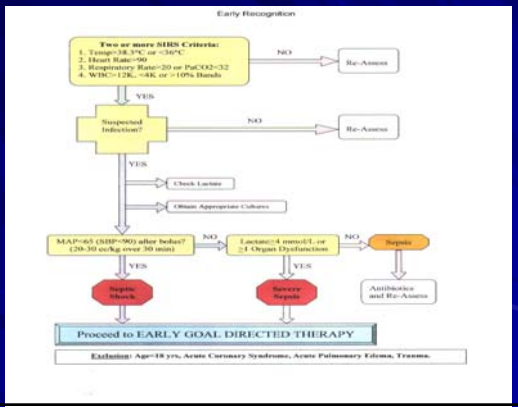
Evidence-Based Sepsis Guidelines

- 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.

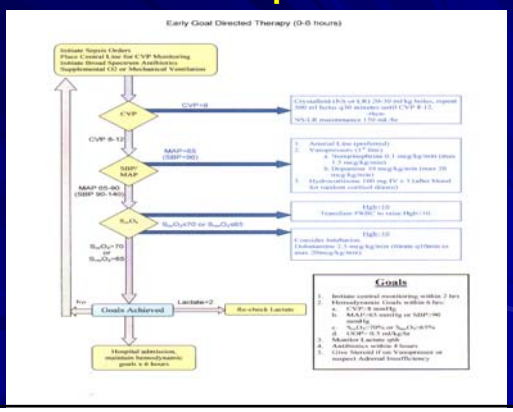
Evidence-Based Sepsis Guidelines

- 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



Evidence-Based Sepsis Guidelines



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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

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Phase 1 Barcelona declaration
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Sponsoring Organizations

- American Association of Critical Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- Australian 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)	Ramsay	Harvey	Sprung
Carlet	Zimmerman	Hazelzet	Torres
Masur	Beale	Hollenberg	Vendor
Gerlach	Bonten	Jorgensen	Bennet
Levy	Brun-Buisson	Maier	Bochud
Vincent	Carcillo	Maki	Cariou
Calandra	Cordonnier	Marini	Murphy
Cohen	Dellinger (EP)	Opal	Nitsun
Gea-Banacloche	Dhainaut	Osborn	Szokol
Keh	Finch	Parrillo	Trzeciak
Marshall	Finfer	Rhodes	Visonneau
Parker	Fourrier	Sevransky	

*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

Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM and the SSC Management Guidelines Committee

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

Table 1. Grading system

Grading of recommendations
- A. Supported by at least two level I investigations
- B. Supported by one level I investigation
- C. Supported by level II investigations only
- D. Supported by at least one level III investigation
- E. Supported by level IV or V evidence

Grading of evidence
- I. Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error of false-negative (beta) error
- II. Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
- III. Nonrandomized, contemporaneous controls
- IV. Nonrandomized, historical controls and expert opinion
- V. Case series, uncontrolled studies, and expert opinion

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

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Table 3. Initial resuscitation and infection issues

Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in parentheses after each guideline
- Indicates a strong recommendation, or "we recommend"
- Indicates a weak recommendation, or "we suggest"

Initial resuscitation (first 6 hrs)
- Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission (1C)
- Resuscitation goals (1C)
  - CVP 8–12 mm Hg*
  - Mean arterial pressure ≥ 65 mm Hg
  - Urine output ≥0.5 mL·kg^{-1}·hr^{-1}
  - Central venous (superior vena cava) oxygen saturation ≥70% or mixed venous ≥65%
- If venous oxygen saturation target is not achieved (2C)
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  - Start dobutamine infusion, maximum 20 μg·kg^{-1}·min^{-1}

Diagnosis
- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)
  - Obtain two or more BCs
  - One or more BCs should be percutaneous
  - One BC from each vascular access device in place >48 hrs
  - Culture other sites as clinically indicated
- Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)

Antibiotic therapy
- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C)
  - Consider combination therapy in *Pseudomonas* infections (2D)
  - Consider combination empiric therapy in neutropenic patients (2D)
  - Combination therapy ≈3–5 days and de-escalation following susceptibilities (2D)
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies (1D)
- Stop antimicrobial therapy if cause is found to be noninfectious (1D)

Source identification and control
- A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 hrs of presentation (1D)
- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C)
- Implement source control measures as soon as possible following successful initial resuscitation (1C) (exception: infected pancreatic necrosis, where surgical intervention is best delayed) (2B)
- Choose source control measure with maximum efficacy and minimal physiologic upset (1D)
- Remove intravascular access devices if potentially infected (1C)

Initial Resuscitation

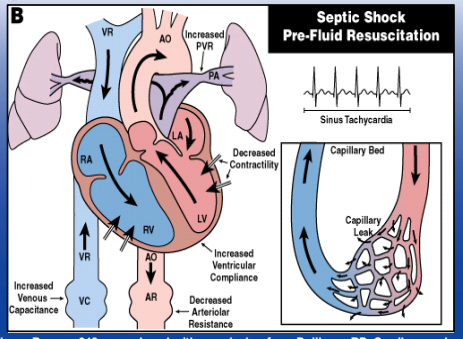
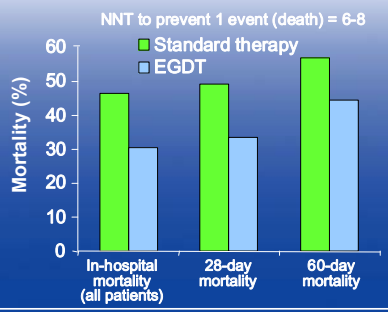


Figure B, page 948, reproduced with permission from Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:946-955.

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



Adapted from Table 3, page 1374, with permission from Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368-1377

Initial Resuscitation

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

	MAP			
	65 mm Hg	75 mm Hg	85 mm Hg	F/LT
Urinary output (mL)	49 ±18	56 ± 21	43 ±13	.60/.71
Capillary blood flow (mL/min/100 g)	6.0 ± 1.6	5.8 ± 11	5.3 ± 0.9	.59/.55
Red Cell Velocity (au)	0.42 ± 0.06	0.44 ±016	0.42 ± 0.06	.74/.97
$Pico_2$ (mm Hg)	41 ± 2	47 ± 2	46 ± 2	.11/.12
Pa-$Pico_2$ (mm Hg)	13 ± 3	17 ± 3	16 ± 3	.27/.40

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

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 [SvO_2] saturation ≥ 70% Central venous ≥ 70% or Mixed venous ≥ 65%

Grade B

Initial Resuscitation

Goals during first 6 hours:

- Central venous or mixed venous O_2 sat < 70% after CVP of 8–12 mm Hg
  - Packed RBCs to Hct 30% and/or
  - Dobutamine to max 20 µg/kg/min

Grade B

Diagnosis

- Appropriate cultures
- Minimum 2 blood cultures
  - 1 percutaneous
  - 1 from each vascular access ≥ 48 hrs

Culture other sites as clinically indicated

Grade D

Antibiotic Therapy

- Begin intravenous antibiotics within first hour of recognition of severe sepsis. and in septic shock.

As early as possible

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.

Grade D

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

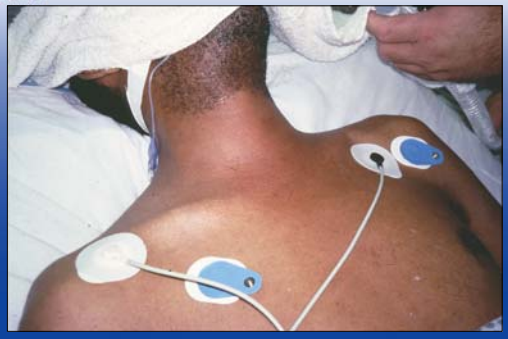
Pseudomonas
Combined therapy in neutropenic patients
Combination ≤ 3-5 days and de-escalating
Duration typically limted to 7-10 days

Grade E

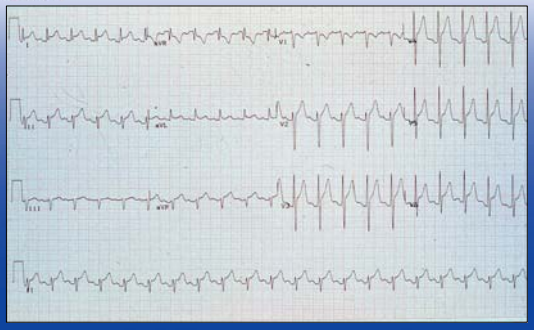
Source Control

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

Grade E



Photograph used with permission from Janice L. Zimmerman, MD



EKG tracing reproduced with permission from Janice L. Zimmerman, MD

Surviving Sepsis Campaign 2008

Fluid Therapy

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

Grade C

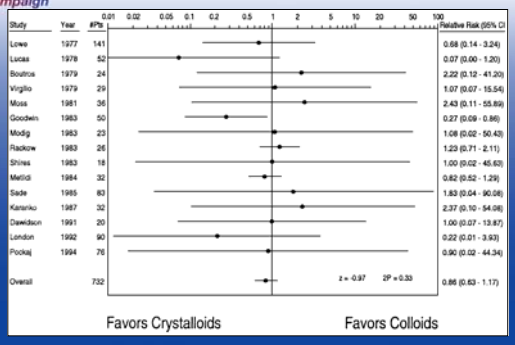


Figure 2, page 206, reproduced with permission from Choi PT, Yip G, Quinonez L, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* 1999; 27:200–210

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, phenylephrineo or vasopressin as the initial vasopressors of choice
Use epinephrine as the first alternative when poorly responsive to norepinephrine

Grade D

Effects of Dopamine, Norepinephrine, and Epinephrine on the Splanchnic Circulation in Septic Shock

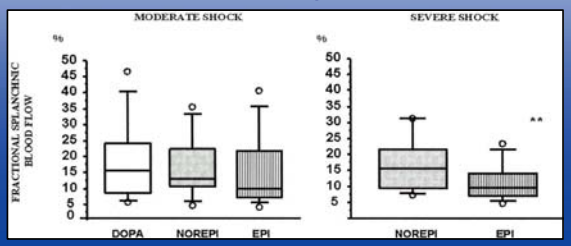


Figure 2, page 1665, reproduced with permission from De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659-1667

Vasopressors

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

Grade B

Bellomo R, et al. *Lancet* 2000; 356:2139-2143

Vasopressors

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

Grade E

Circulating Vasopressin Levels in Septic Shock

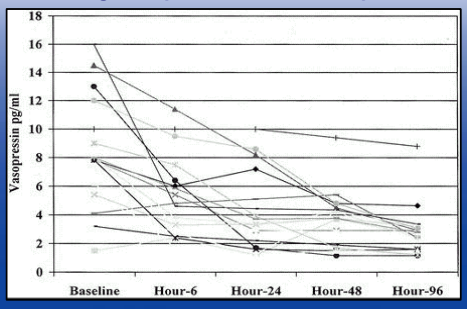


Figure 2, page 1755 reproduced with permission from Sharshar T, Blanchard A, Paillard M, et al. Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752-1758

Vasopressin and Septic Shock

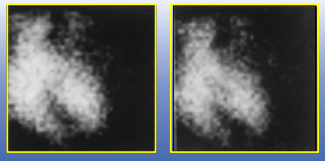
- Versus cardiogenic shock
- Decreases or eliminates requirements of traditional pressors
- As a pure vasopressor expected to decrease cardiac output

Vasopressors
Vasopressin

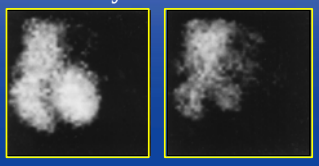
- Not a replacement for norepinephrine or dopamine as a first-line agent
- Consider in refractory shock despite high-dose conventional vasopressors
- If used, administer at 0.01-0.04 units/minute in adults 0.03 units/minute

Grade E

During Septic Shock

Diastole  Systole

10 Days Post Shock

Diastole  Systole

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

Yu, et al. *CCM* 1993; 21:830-838
Hayes, et al. *NEJM* 1994; 330-1717-1722
Gattinoni, et al. *NEJM* 1995; 333:1025-1032

Steroid Therapy

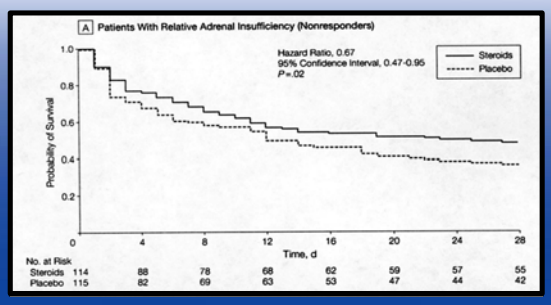


Figure 2A, page 867, reproduced with permission from Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871

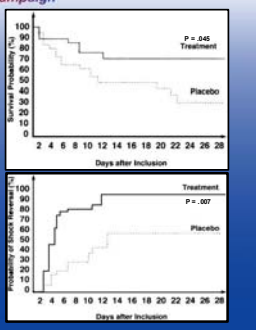


Figure 2 and Figure 3, page 648, reproduced with permission from Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med 1998; 26:645-650*

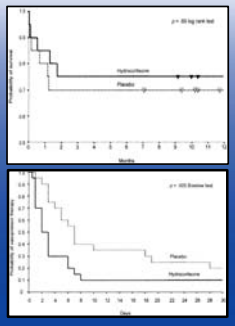


Figure 2 and Figure 3, page 727, reproduced with permission from Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723-732

- 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

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

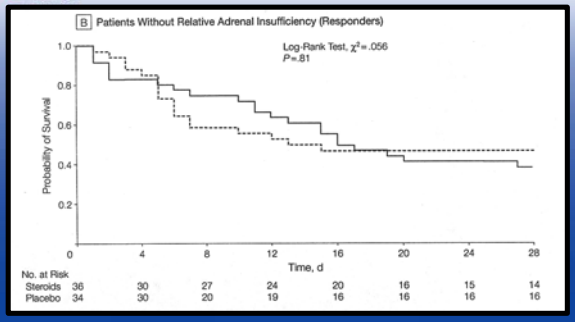


Figure 2B, page 867, reproduced with permission from Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871

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

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

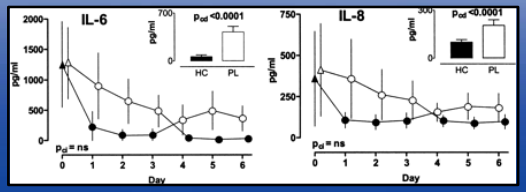


Figure 3, page 515, reproduced with permission from Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low dose" hydrocortisone in septic shock. *Am J Respir Crit Care Med* 2003;167:512-520

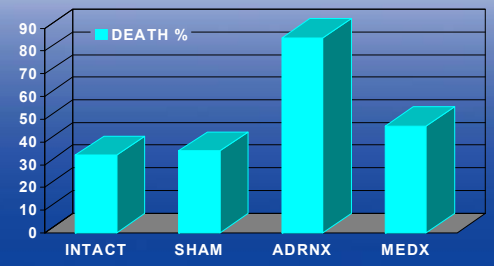
Steroids

Optional:

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

Grade E

ADRENALS AND SURVIVAL FROM ENDOTOXEMIA



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* 1995; 3:434-439

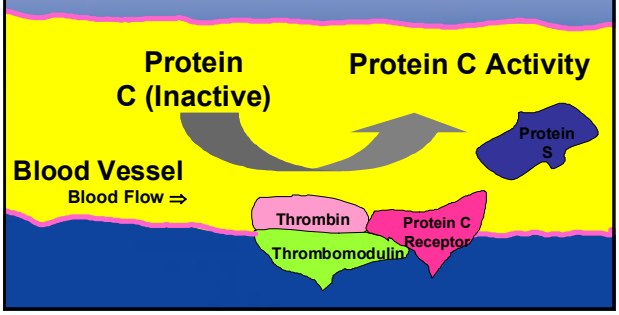
Steroids

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

Grade A

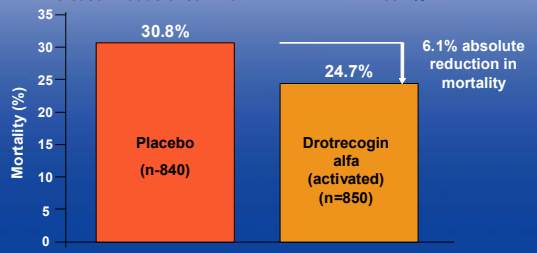
Bone, et al. NEJM 1987; 317-658
VA Systemic Sepsis Cooperative Study Group. NEJM 1987; 317:659-665

Human Activated Protein C Endogenous Regulator of Coagulation



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%

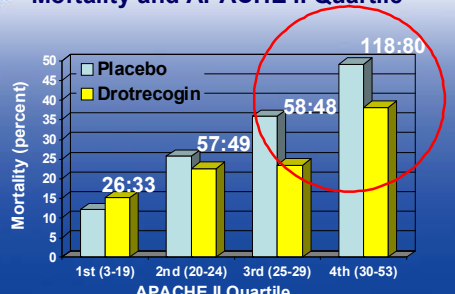


Adapted from Table 4, page 704, with permission from Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699-709

Patient Selection for rhAPC

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

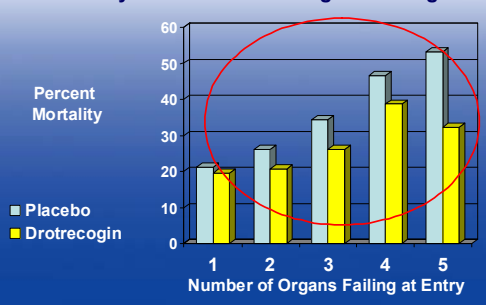
Mortality and APACHE II Quartile



*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

Mortality and Numbers of Organs Failing



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

Transfusion Strategy in the Critically Ill

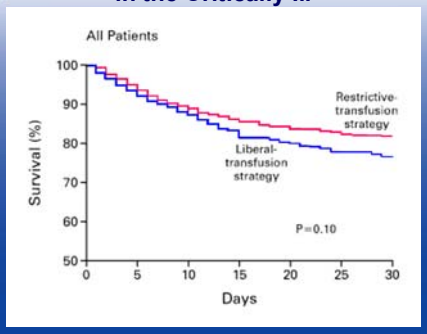


Figure 2A, page 414, reproduced with permission from Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409-417

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; 1869-1878

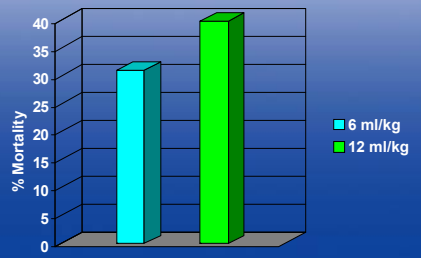
Blood Product Administration

- Platelet administration
  - Transfuse for < 5000/mm^3 -
  - Transfuse for 5000/mm^3 – 30,000/mm^3 with significant bleeding risk
  - Transfuse < 50,000/mm^3 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;342:1301-1378*

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 H_20

Grade B

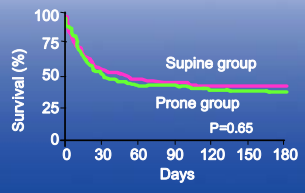
Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- 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 (≤88)
  - Prone – 23.1%
  - Supine – 47.2%



Kaplan-Meier estimates of survival at 6 months

Gattinoni L, et al. *N Engl J Med* 2001;345:568-73; Slutsky AS. *N Engl J Med* 2001;345:610-2.

The Role of Prone Positioning in ARDS

Consider prone positioning in ARDS when:

- Potentially injurious levels of F_1O_2 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; 354:1851-1858

Mechanical Ventilation of Septic Patients

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

Grade A

Ely, et al. NEJM 1996; 335:1864-1869
Esteban, et al. AJRCCM 1997; 156:459-465
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 H_2O
- T-piece

Prior to SBT

a) Arousable
b) Hemodynamically stable (without vasopressor agents)
c) No new potentially serious conditions
d) Low ventilatory and end-expiratory pressure requirements
e) Requiring levels of FIO_2 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

Grade B

Kollef, et al. Chest 1998; 114:541-548
Brook, et al. CCM 1999; 27:2609-2615
Kress, et al. NEJM 2000; 342:1471-1477

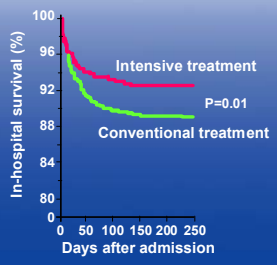
Neuromuscular Blockers

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

Grade E

The Role of Intensive Insulin Therapy in the Critically Ill

- At 12 months, intensive insulin therapy reduced mortality by 3.4% (P<0.04)



Adapted from Figure 1B, page 1363, with permission from van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001;345:1359-67

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

Grade D

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

Cooper, et al. Ann Intern Med 1990; 112:492-498
Mathieu, et al. CCM 1991; 19:1352-1356

Changing pH Has Limited Value

Treatment	Before	After
NaHCO3 (2 mEq/kg)		
pH	7.22	7.36
PAOP	15	17
Cardiac output	6.7	7.5
0.9% NaCl		
pH	7.24	7.23
PAOP	14	17
Cardiac output	6.6	7.3

Cooper DJ, et al. *Ann Intern Med 1990; 112:492-498*

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

Cook DJ, et al. *Am J Med* 1991; 91:519-527

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.**

Grade E

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

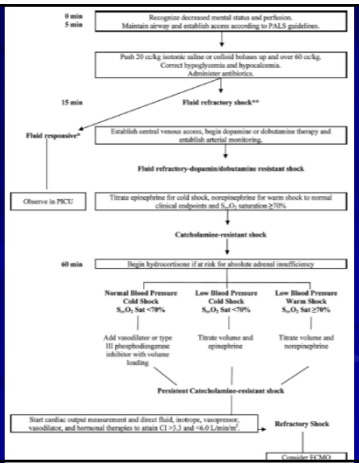
Therapeutic Endpoints

- **Capillary refill < 2 sec**
- **Warm extremities**
- **Urine output > 1 ml/kg/hr**
- **Normal mental status**
- **Decreased lactate**
- **Central venous O_2 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.**

Surviving Sepsis Campaign 2008: Pediatric



Surviving Sepsis Campaign

Surviving Sepsis

Phase 1 Barcelona declaration

Phase 2 Evidence based guideline

Phase 3 Implementation and education

Surviving Sepsis Campaign

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

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Sepsis Resuscitation Bundle

- 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.

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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

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

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Sepsis Management Bundle

- Glucose control maintained ≥ lower limit of normal, but < 150 mg/dl (8.3 mmol/L)
- Inspiratory plateau pressures maintained < 30 cm H_2O for mechanically ventilated patients.

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 ($ScvO_2$) of ≥ 70%**

**Achieving a mixed venous oxygen saturation (SvO_2) 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

Actual title of painting is "Hercules Kills Cerberus," by Renato Pettinato, 2001. Painting hangs in Zuccaro Place in Agira, Sicily, Italy. Used with permission of artist and the Rubolotto family.

www.survivingsepsis.org

♦ ♦ ♦

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Acknowledgment

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