Updates in Sepsis Management

Ruth M. Kleinpell PhD RN FCCM
Rush University Medical Center
Chicago Illinois USA
Sepsis

- Sepsis is a complex condition that occurs as a result of the systemic manifestation of infection.
- Severe sepsis, which occurs when sepsis progresses to involve acute organ system dysfunction, contributes to increased severity of illness, length of stay and mortality rates of 20% to 50%.

Sepsis

- Sepsis initiates an excessive inflammatory response that is characterized by:
  - Hemodynamic derangements including arterial hypotension, peripheral vasodilation, hypovolemia from capillary leak and myocardial depression

Endothelial damage  \(\uparrow\)  Capillary permeability & edema formation  \(\Rightarrow\)  Organ system dysfunction

Waxman AB et al Crit Care 2009: 9:1; http://ccforum.coi/content/9/1E1
Pathogenic insult resulting in infection

Microthrombi formation

Endothelial damage

↑ Capillary permeability and edema formation

Enhanced expression of adhesion molecules

Massive cytokine production

Effector molecule release

Inflammatory/Immune System Response

Specific genetic signaling

Neutrophil and Monocyte activation

Endothelial cell activation

Platelet dysfunction

Quadrad of dysfunction in sepsis

↑ Coagulation

↓ Fibrinolysis

Apoptosis

Imbalance between inflammation and antiinflammation

Reduced tissue/cellular perfusion

Organ dysfunction

Oxygen & substrate debt

Insult phase

Molecular activation phase

System dysfunction phase

Organ dysfunction phase

Insult phase

Molecular activation phase

System dysfunction phase

Organ dysfunction phase

Microthrombi formation

Endothelial damage

↑ Capillary permeability and edema formation
Surviving Sepsis Campaign

Guidelines for Management of Severe Sepsis/Septic Shock

2008
Surviving Sepsis Campaign

Guidelines for Management of Severe Sepsis/Septic Shock

2012

R. Phillip Dellinger, MD1; Mitchell M. Levy, MD2; Andrew Rhodes, MB BS3; Djillali Annane, MD4; Herwig Gerlach, MD, PhD5; Steven M. Opal, MD6; Jonathan E. Sevransky, MD7; Charles L. Sprung, MD8; Ivor S. Douglas, MD9; Roman Jaeschke, MD10; Tiffany M. Osborn, MD, MPH11; Mark E. Nunnally, MD12; Sean R. Townsend, MD13; Konrad Reinhart, MD14; Ruth M. Kleinpell, PhD, RN-CS15; Derek C. Angus, MD, MPH16; Clifford S. Deutschman, MD, MS17; Flavia R. Machado, MD, PhD18; Gordon D. Rubenfeld, MD19; Steven A. Webb, MB BS, PhD20; Richard J. Beale, MB BS21; Jean-Louis Vincent, MD, PhD22; Rui Moreno, MD, PhD23; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

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

**Design:** A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict of interest policy was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.
Evidence-based recommendations
Outline the management of severe sepsis and septic shock
Identify key recommendations for treatment

The GRADE system
Grade 1 – Strong
Grade 2 – Weak

Quality of Evidence:
Grade A – High
Grade B – Moderate
Grade C – Low
Grade D – Very Low

Grading of Recommendations Assessment, Development and Evaluation

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Initial Resuscitation

1. We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration 4 mmol/L).

During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

- Central venous pressure (CVP): 8–12mm Hg
- Mean arterial pressure (MAP) ≥ 65mm Hg
- Urine output ≥ 0.5mL.kg–1.hr –1
- Central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65%, respectively

(Grade 1C)
Antibiotic therapy

1. We recommend that intravenous antimicrobial therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (grade 1C).

2. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) (grade 1B).
Fluid therapy

1. We recommend crystalloids be used in the initial fluid resuscitation in patients (Grade 1B).

2. We recommend that initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30ml/kg. (Grade 1C).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Fluid therapy

3. We suggest adding albumin in the initial fluid resuscitation regimen of severe sepsis and septic shock when patients require substantial amounts of crystalloids (Grade 2C).

4. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (Grade 1B)

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Vasopressors

1. We recommend that vasopressor therapy initially target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).

2. We recommend norepinephrine as the first choice vasopressor (Grade 1 B).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
3. We recommend epinephrine (added or substituted) when an additional agent is needed to maintain adequate blood pressure (Grade 2B).

4. We suggest vasopressin 0.03 units/minute can be added to or substituted for norepinephrine (Ungraded).
Vasopressors

6. We recommend that low-dose dopamine not be used for renal protection (grade 1A).

7. We recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (Ungraded).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Inotropic Therapy

1. We recommend that a dobutamine infusion be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate mean arterial pressure. (grade 1C).

2. We recommend against the use of a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Diagnosis

1. We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in antimicrobial administration.

2. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antimicrobial therapy with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hr.) inserted (1C)

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Antibiotic therapy

3. The antimicrobial regimen should be reassessed daily to optimize activity, to prevent the development of resistance, to reduce toxicity, and to reduce costs. (grade 1B)

4. We suggest the use of low procalcitonin levels to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found (grade 2C).
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥ 8 mm Hg, ScvO₂ of ≥ 70%, and normalization of lactate.
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

METHODS
In 31 emergency departments in the United States, we randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based EGDT; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. The primary end point was 60-day in-hospital mortality.

RESULTS
We enrolled 1341 patients, of whom 439 were randomly assigned to protocol-based EGDT, 446 to protocol-based standard therapy, and 456 to usual care.

There were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support.
A  Cumulative In-Hospital Mortality to 60 Days

P=0.52 by log-rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Protocol-based EGDT</th>
<th>Protocol-based standard therapy</th>
<th>Usual care</th>
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<td>439</td>
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Figure 2. Cumulative Mortality.
Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.
Surviving Sepsis Campaign Responds to ProCESS Trial
Updated 19 May 2014

The Surviving Sepsis Campaign (SSC) has received many inquiries regarding the recent publication of the Protocol-Based Care for Early Septic Shock (ProCESS) trial’s effect on the continuing activities of the Campaign. (1)

(1) The ProCESS trial reflects the consensus that early diagnosis of septic shock is essential. Notably, all groups in the study received on average more than 2 liters of fluid prior to randomization and more than 75% received antibiotics prior to randomization—both elements of the 3-hour Surviving Sepsis Campaign bundle. (2) The editorial accompanying the ProCESS study highlights these points. (3)

(2) The 18% mortality rate in the “usual care” arm of ProCESS illustrates a dramatic change in the management and outcomes of patients with septic shock. (1) In comparison, septic shock mortality was 46.5% in the 2001 early goal-directed therapy trial by Rivers. (4)

(3) Given the remarkably low mortality rate in the control arm of ProCESS, and the pending results of 2 large ongoing trials (the Australian Resuscitation In Sepsis Evaluation Randomised Controlled Trial [ARISE] and The Protocolised Management in Sepsis Trial [ProMISE]), the SSC will determine any appropriate revisions to the bundle elements when these study results are available.
Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*

Karthik Raghunathan, MD, MPH; Andrew Shaw, MB, FRCA, FFICM, FCCM; Brian Nathanson, PhD; Til Stürmer, MD, PhD; Alan Brookhart, PhD; Mihaela S. Stefan, MD; Soko Setoguchi, MD, DrPH; Chris Beadles, MD, PhD; Peter K. Lindenauer, MD, MSc

**Objective:** Isotonic saline is the most commonly used crystalloid in the ICU, but recent evidence suggests that balanced fluids like Lactated Ringer’s solution may be preferable. We examined the association between choice of crystalloids and in-hospital mortality during the resuscitation of critically ill adults with sepsis.

**Setting:** Three hundred sixty U.S. hospitals that were members of the Premier Healthcare alliance between November 2005 and December 2010.

**Patients:** A total of 53,448 patients with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 including 3,396 (6.4%) that received balanced fluids.
**TABLE 1. Association Between Resuscitation With Balanced Fluids and Primary and Secondary Outcomes in Propensity-Matched Cohorts**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Balanced Fluid-Matched Cohort</th>
<th>No-Balanced Fluid-Matched Cohort</th>
<th>Effect Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute in-hospital mortality</td>
<td>19.6% (659 of 3,365)</td>
<td>22.8% (768 of 3,365)</td>
<td>Relative risk, 0.86</td>
<td>0.78, 0.94; <em>p</em> = 0.001</td>
</tr>
<tr>
<td>ARF with dialysis</td>
<td>4.52% (142 of 3,144)</td>
<td>4.74% (149 of 3,144)</td>
<td>Relative risk, 0.953</td>
<td>0.761, 1.194</td>
</tr>
<tr>
<td>ARF without dialysis</td>
<td>7.12% (159 of 2,655)</td>
<td>7.50% (199 of 2,655)</td>
<td>Relative risk, 0.950</td>
<td>0.784, 1.150</td>
</tr>
<tr>
<td>Hospital LOS in days (survivors)</td>
<td>11.26</td>
<td>11.37</td>
<td>Absolute difference, −0.11</td>
<td>−0.55, 0.34</td>
</tr>
<tr>
<td>ICU LOS in days (survivors)</td>
<td>5.39</td>
<td>5.50</td>
<td>Absolute difference, −0.11</td>
<td>−0.37, 0.15</td>
</tr>
</tbody>
</table>

ARF = acute renal failure, LOS = lengths of stay.
Figure 3. The x-axis categorizes patients based on quintiles of the total fluid volume received (median total volume in Q1 = 2.5 L, Q2 = 4 L, Q3 = 5.5 L, Q4 = 7 L, and Q5 = 10.5 L). The y-axis shows the adjusted in-hospital mortality. Patients receiving balanced fluids had a lower absolute mortality rate regardless of the total amount of fluid received. Patients receiving balanced fluids have lower mortalities, with significant differences within the lowest and highest quintiles.
Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day. (Grade 2C).

2. We recommend that corticosteroids not be administered for the purpose of treating severe sepsis in the absence of shock (Grade 1D).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)

1. We recommend that clinicians target a tidal volume of 6 mL/kg versus 12 ml/kg (predicted) body weight in patients with sepsis-induced ARDS (grade 1A).
   1. Plateau pressures $\leq 30\text{cm H}_2\text{O}$ (grade 1B)
   2. Use of PEEP at end expiration to avoid alveolar collapse (grade 1B)
   3. Recruitment maneuvers for severe refractory hypoxemia (grade 2C)
   4. Prone positioning for $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 100\ \text{mm Hg}$ in facilities that have experience in such practices (grade 2B)

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. We recommend that either continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (Grade 1B).

2. We recommend that NMBAs be avoided if possible in the septic patient without ARDS due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of depth of blockade should be used (Grade 1C).

3. We suggest a short course of NMBA (< 48 hours) for patients with ARDS early, sepsis induced ARDS and PaO₂/FIO₂ ratio ≤ 150 mmHg (Grade 2C).

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Glucose control

1. We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose ≤ 180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (Grade 1A).

2. We recommend that blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (Grade 1C).
Surviving Sepsis Campaign 2012 Guidelines - Glucose Control

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

Annane D. COIITSS. *JAMA.* 2010;303:341–348

Supportive Therapies

1. Blood product administration
2. Renal replacement
3. Stress ulcer prophylaxis
4. Deep vein thrombosis prophylaxis
5. Nutrition

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
Blood Product Administration

• We recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL in adults (grade 1B).

Dellinger RP et al Crit Care Med 2008; 36:296-437
Blood Product Administration

• In patients with severe sepsis, we suggest that platelets be administered prophylactically when counts are ≤ 10,000/mm³ in the absence of apparent bleeding,

• as well as when counts are ≤ 20,000/mm³ if the patient has a significant risk of bleeding.

• Higher platelet counts (≥ 50,000/mm³ are advised for active bleeding, surgery, or invasive procedures (grade 2D).
Renal Replacement Therapy

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

• We suggest the use of continuous therapies to facilitate the management of fluid balance in hemodynamically unstable septic patients (grade 2D)
Deep vein thrombosis prophylaxis

• We recommend that patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B).

• We recommend that this be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus unfractionated heparin (UFH) twice daily
Deep vein thrombosis prophylaxis

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

- We suggest that patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
Stress Ulcer Prophylaxis

- We recommend that stress ulcer prophylaxis using H\(_2\) blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).

- When stress ulcer prophylaxis is used, we suggest the use of proton pump inhibitors rather than H\(_2\) receptor antagonists (grade 2C).
1. We suggest administering oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock. (Grade 2C).

2. We suggest avoiding mandatory full caloric feeding in the first week, but rather suggest low-dose feeding (eg. up to 500 kcal/day), advancing only as tolerated (Grade 2B).
Nutrition

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

Dellinger RP et al. Critical Care Medicine 2013;41:580-637
2008 Surviving Sepsis Campaign Guidelines

- Consideration for limitation of support (1D)
  - Discuss end-of-life care for critically ill patients
  - Promote family communication to discuss use of life-sustaining therapies

1D = Very Low Quality of Evidence
Recommendation: Change from 1D - a very low grade of evidence- to 1B - a moderate degree of evidence

Rationale: Growing number of studies published since the last guidelines which substantiate the importance of identifying goals of care, discussing prognosis, and integrating palliative and end-of-life care concepts.
Setting Goals of Care

- Recommendation 1: We recommend that identification of goals of care, prognosis for achieving those goals and the level of certainty for the prognosis be discussed with patients and families (grade 1B).
- Recommendation 2: We recommend that these communications should be incorporated into treatment plans with integration of palliative care principles, and as appropriate, end-of-life care planning (grade 1B).
- Recommendation 3: It is suggested that goals of care be addressed as early as feasible but no later than within 72 hours (grade 2C).
New Focus Area

• Screening for Sepsis & Performance Improvement
  – We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (grade 1C).
  – Performance improvement efforts in severe sepsis should be used to improve patient outcomes (UG).

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Summary: Optimizing Outcomes in Severe Sepsis

- Role of Astute Clinical Assessment
- **EARLY:**
  - Recognition
  - Treatment
- Appropriate Therapy Use