Surviving Sepsis Guidelines: Critical Evaluation

Dr. Bert Vandewiele
Fellow Critical Care SBAH
21 February 2011
Overview

• Definitions (SIRS, Sepsis, Severe Sepsis, Septic Shock)
• Evidence Grading: GRADE System
• Evidence 1 A recommendations !!!
• Revised version 2008: recommendations and reflexions per category (total 18)
Definitions

**Definitions**

- SIRS > 1 of the following
  - Temperature
    - <36°C
    - >38°C
  - Heart Rate > 90/min
  - Respiratory Rate > 20 / min
  - pCO2 < 32 mmHg
  - WCC
    - < 4000 mm³
    - > 12000 mm³
    - > 10% immature cells

**Sepsis**
- SIRS + Infection
  - Septicemia
  - Bacteremia
  - Fungemia
  - Viremia
  - Parasitemia

---

Figure 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.
Definitions

• Severe Sepsis
  – Sepsis + sepsis induced organ dysfunction
  – Sepsis + tissue hypoperfusion
    • Oliguria
    • Lactic acidosis
    • Acute alteration in mental state
  – Sepsis + Hypotension
    • Systolic Blood Pressure (SBP) < 90 mmHg
    • Mean Arterial Pressure (MAP) < 70 mmHg
    • SBP decrease > 40 mmHg or < 2SD below normal for age
    • In the absence of other causes of hypotension
• Septic Shock = Sepsis induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities

GRADE System

• Grades of
• Recommendation
• Assessment
• Development and
• Evaluation

GRADE System

• To guide assessment of quality of evidence
  – from high (A) to very low (D).
• To determine the strength of recommendations.
  – A strong recommendation (1) indicates that an intervention’s desirable effects clearly outweigh its undesirable effects (risk, burden, cost), or clearly do not.
  – Weak recommendations (2) indicate that the tradeoff between desirable and undesirable effects is less clear.

• The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence.
GRADE system

• Underlying methodology
  – A  RCT
  – B  Downgraded RCT or upgraded observational studies
  – C  Well-done observational studies
  – D  Case series or expert opinion

Factors that may decrease the strength of evidence
1. Poor quality of planning and implementation of available RCTs suggesting high likelihood of bias
2. Inconsistency of results (including problems with subgroup analyses)
3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
4. Imprecision of results
5. High likelihood of reporting bias

Factors that may increase the strength of evidence
1. Large magnitude of effect (direct evidence, relative risk (RR) > 2 with no plausible confounders)
2. Very large magnitude of effect with RR > 5 and no threats to validity (by two levels)
3. Dose response gradient
GRADE System

• Factors determining strong vs weak Recommendations

The lower the quality of evidence the less likely a strong recommendation. If values and preferences vary widely, a strong recommendation becomes less likely. The higher the risk, the greater the magnitude of benefit. Larger relative risk reductions or larger increases in relative risk of harm make a strong recommendation more or less likely respectively. The larger the absolute benefits and harms, the greater or lesser likelihood respectively of a strong recommendation. The greater the precision the more likely is a strong recommendation. The higher the cost of treatment, the less likely a strong recommendation.

## Classification of guidelines

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strong recommendation</th>
<th>Weak Recommendation</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRADE A</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>11%</td>
</tr>
<tr>
<td>GRADE B</td>
<td>17</td>
<td>7</td>
<td>24</td>
<td>32%</td>
</tr>
<tr>
<td>GRADE C</td>
<td>18</td>
<td>8</td>
<td>26</td>
<td>34%</td>
</tr>
<tr>
<td>GRADE D</td>
<td>11</td>
<td>7</td>
<td>18</td>
<td>24%</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>22</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>71%</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11/3/2011

Bert Vandewiele
GRADE 1A Recommendations: 11%

- Do not use low dose dopamine for renal protection (2001)
- Hydrocortisone dose should be ≤ 300mg/day (1987)
- Adult patients with severe sepsis and low risk of death should not receive rhAPC (2005)
- Use a weaning protocol and a spontaneous breathing trial regularly to evaluate the potential for discontinuing mechanical ventilation (1996)
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (2003)
- Use either low dose UFH or LMWH unless contraindicated (1981)
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated. (1989)
- Provide stress ulcer prophylaxis using H2 blocker (1998)
Do not use low dose dopamine for renal protection

Hydrocortisone dose should be \( \leq 300 \text{mg/day} \)

The New England Journal of Medicine

©Copyright, 1987, by the Massachusetts Medical Society

Volume 317  SEPTEMBER 10, 1987  Number 11

A CONTROLLED CLINICAL TRIAL OF HIGH-DOSE METHYLPREDNISOLONE IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Roger C. Bone, M.D., Charles J. Fisher, Jr., M.D., Terry P. Clemmer, M.D., Gus J. Slotman, M.D., Craig A. Metz, M.S., Robert A. Balk, M.D., and the Methylprednisolone Severe Sepsis Study Group

Abstract  The use of high-dose corticosteroids in the treatment of severe sepsis and septic shock remains controversial. Our study was designed as a prospective, randomized, double-blind, placebo-controlled trial of high-dose methylprednisolone sodium succinate for severe sepsis and septic shock. Diagnosis was based on the clinical suspicion of infection plus the presence of fever or hypothermia (rectal temperature \( > 38.3^\circ \text{C} \) [\( 101^\circ \text{F} \)] or \( < 35.6^\circ \text{C} \) [\( 96^\circ \text{F} \)], tachypnea (\( > 20 \) breaths per minute), tachycardia (\( > 90 \) beats per minute), and the presence of one of the following indications of organ dysfunction: a change in mental status, hypoxemia, elevated lactate levels, or oliguria. Three hundred eighty-two patients were enrolled. Treatment — either methylprednisolone sodium succinate (30 mg per kilogram of body weight) or placebo — was given in four infusions, starting within two hours of diagnosis.

No significant differences were found in the prevention of shock, the reversal of shock, or overall mortality. In the subgroup of patients with elevated serum creatinine levels (>2 mg per deciliter) at enrollment, mortality at 14 days was significantly increased among those receiving methylprednisolone (46 of 78 [59 percent] vs. 17 of 58 [29 percent] among those receiving placebo; P<0.01). Among patients treated with methylprednisolone, significantly more deaths were related to secondary infection.

We conclude that the use of high-dose corticosteroids provides no benefit in the treatment of severe sepsis and septic shock. (N Engl J Med 1987; 317:653-8.)

Steroids And Surviving Sepsis Campaign

- Consider intravenous hydrocortisone for adult septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors. *(2C)*
- ACTH stimulation test is **not recommended** to identify the subset of adults with septic shock who should receive hydrocortisone. *(2B)*
- Hydrocortisone is preferred to dexamethasone. *(2B)*
- Fludrocortisone (50μg orally once a day) may be included if an alternative to hydrocortisone is being used which lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used. *(2C)*
- Steroid therapy may be weaned once vasopressors are no longer required. *(2D)*
- **Hydrocortisone dose should be ≤300 mg/day.** *(1A)*
- **Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it.** *(1D)*
Results One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 34; corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P = .02). Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; P = .001). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

Methods
In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.

Conclusions
Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)

Adult patients with severe sepsis and low risk of death should not receive rhAPC

- We suggest that adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have APACHE II ≥ 25 or multiple organ failure, receive rhAPC if there are no contraindications (Grade 2B except for patients within 30 days of surgery where it is Grade 2C). Relative contraindications should also be considered in decision making.

- We recommend that adult patients with severe sepsis and low risk of death, most of whom will have APACHE II < 20 or one organ failure, do not receive rhAPC (Grade 1A).
"This new wonder drug is meant to keep the patient alive long enough to pay their bill."
Recombinant Human Activated Protein C

• **PROWESS**
  - Stopped early for **efficacy**
    - 1690 patients
    - 6.1% absolute total mortality reduction
    - Better risk reduction in sicker patients

• **ADDRESS**
  - Stopped early for **futility**
    - 2613 patients
    - 28-day mortality 17% placebo vs 18.5% on APC
    - Patients with low risk of death at time of enrollment

---


Use a weaning protocol and a spontaneous breathing trial regularly to evaluate the potential for discontinuing mechanical ventilation.

**Results** Although the 149 patients randomly assigned to the intervention group had more severe disease, they received mechanical ventilation for a median of 4.5 days, as compared with 6 days in the 151 patients in the control group (P = 0.003). The median interval between the time a patient met the screening criteria and the discontinuation of mechanical ventilation was one day in the intervention group and three days in the control group (P < 0.001).

Complications — removal of the breathing tube by the patient, reintubation, tracheostomy, and mechanical ventilation for more than 21 days — occurred in 20 percent of the intervention group and 41 percent of the control group (P = 0.001). The number of days of intensive care and hospital care was similar in the two groups. Total costs for the intensive care unit were lower in the intervention group (median, $15,740, vs. $20,890 in the controls; P = 0.03); hospital costs were lower, though not significantly so (median, $26,229 and $29,048, respectively; P = 0.3).

**Conclusions** Daily screening of the respiratory function of adults receiving mechanical ventilation, followed by trials of spontaneous breathing in appropriate patients and notification of their physicians when the trials were successful, can reduce the duration of mechanical ventilation and the cost of intensive care and is associated with fewer complications than usual care. (N Engl J Med 1996;335:1864-9.)
Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS.
Swan Ganz catheters

• Pitfalls
  1. Measures pressures, not volumes.
  2. Differences in interpretation of results
  3. Lack of correlation of PAOP with clinical response
  4. Absence of a proven strategy to use catheter results

• Well-selected patients remain appropriate candidates for pulmonary artery catheter insertion when the answers to important management decisions depend on information only obtainable from direct measurements made within the pulmonary artery.

Deep Vein Trombosis Prophylaxis

• Use either low dose UFH or LMWH unless contraindicated.
  – LMWH in very high risk (superior)
  – UFH in renal failure (12 hourly or 8 hourly?)

• Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated.

Prophylaxis Against Deep Vein Thrombosis in Critically Ill Patients With Severe Renal Insufficiency With the Low-Molecular-Weight Heparin Dalteparin

An Assessment of Safety and Pharmacokinetics

James Douketis, MD, FRCPC; Deborah Cook, MD, MSc; Gordon Guyatt, MD, FRCP(C); William Geerts, MD, FRCPC; John Granton, MD, FRCPC; Paul Hebert, MD, FRCPC; Robert Fowler, MD, FRCPC; Andreas Freitag, MD, FRCPC; David Anderson, MD, FRCPC; Nicole Zytxarak, MSc; for the Canadian Critical Care Trials Group

Results: We enrolled 156 patients with a mean (SD) creatinine clearance of 18.9 (6.5) mL/min; 18 were excluded because they died or were discharged before testing (n=3) or had prevalent DVT (n=15). Of 138 patients included, the median (interquartile range [IQR]) duration was 10 (5-17) days. Bioaccumulation was defined by a trough anti-Xa level higher than 0.40 IU/mL, measured twice weekly. The pharmacodynamic properties of dalteparin were assessed by serial anti-Xa levels measured on days 3, 10, and 17.

Conclusion: In critically ill patients with severe renal insufficiency, DVT prophylaxis with dalteparin sodium, 5000 IU once daily, is not associated with an excessive anticoagulant effect due to drug bioaccumulation and is unlikely to contribute to bleeding.
Stress Ulcer Prophylaxis

- No study performed specifically in patients with severe sepsis
- No mortality benefit proven, though reduction in clinically significant upper GI bleed
Stress Ulcer Prophylaxis

• H2 preference above sulcrafate

• Equivalency between H2 blokkers and PPI
GRADE 1A Recommendations: 11%

- Do not use low dose dopamine for renal protection (2001)
- Hydrocortisone dose should be ≤ 300mg/day (1987)
- Adult patients with severe sepsis and low risk of death should not receive rhAPC (2005)
- Use a weaning protocol and a spontaneous breathing trial regularly to evaluate the potential for discontinuing mechanical ventilation (1996)
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (2003)
- Use either low dose UFH or LMWH unless contraindicated (1981)
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated. (1989)
- Provide stress ulcer prophylaxis using H2 blocker (1998)
Table 3 Initial Resuscitation and Infection Issues

<table>
<thead>
<tr>
<th>Initial resuscitation (first 6 hours)</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
<th>have been assessed using the GRADE criteria, presented in brackets after each guideline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Include in all patients with hypovolemia or elevated mean arterial BP &gt; 4 mmHg, do not delay pending ICU admission.</td>
<td>Strong recommendation</td>
<td>High quality evidence</td>
<td></td>
</tr>
<tr>
<td>- Central venous pressure (CVP) 8-12 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean arterial pressure &gt; 60 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Central venous saturation &gt; 70%, or mixed venous PO2 &gt; 65 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- If mixed venous PO2 saturation target not achieved, consider further fluid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Transfuse packed red blood cells if required to hematocrit of ≥ 30% and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dobutamine infusion max 20 mcg/kg/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A higher target CVP of 12-15 mmHg is recommended in the presence of mechanical ventilation or pre-existing decreased ventricular compliance.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Hemodynamic Support and Adjunctive Therapy

<table>
<thead>
<tr>
<th>Fluid therapy</th>
<th>Strengthen the communication and quality of evidence have been assessed using the GRADE criteria, presented in brackets after each guideline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fluid resuscitation using crystalloids or colloids.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>- Target a CVP of 8-12 mm Hg, or if mechanically ventilated,</td>
<td></td>
</tr>
<tr>
<td>- Use a fluid challenge protocol associated with a hemodynamic improvement.</td>
<td></td>
</tr>
<tr>
<td>- Give fluid challenges of 100 ml of crystalloids or 300-500 ml of colloids over 30 minutes, and repeat if necessary to maintain a CVP of 8-12 mm Hg.</td>
<td></td>
</tr>
<tr>
<td>- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement.</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Supportive Therapy of Severe Sepsis

<table>
<thead>
<tr>
<th>Blood product administration</th>
<th>Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in brackets after each guideline.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Give red blood cells when hematocrit decreases to &lt; 7.0 g/dL (70 g/L) to target a hematocrit of 7.0-9.0 g/dL in adults.</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>- A hematocrit level may be required in special circumstances (e.g., myocutaneous ischemia, severe hypotension, acute bleeding).</td>
<td></td>
</tr>
<tr>
<td>- Do not use erythropoiesis to treat severe anemia. Erythropoietin may be used for other accepted reasons.</td>
<td></td>
</tr>
<tr>
<td>- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is an indication for planned invasive procedures.</td>
<td></td>
</tr>
<tr>
<td>- Do not use anticoagulants</td>
<td></td>
</tr>
<tr>
<td>- Administer platelets when</td>
<td></td>
</tr>
<tr>
<td>- Platelet counts &lt; 50,000/mm³ (5 x 10⁹/L) regardless of bleeding.</td>
<td></td>
</tr>
<tr>
<td>- Platelet counts 50,000-30,000/mm³ (5-3 x 10⁹/L) and there is significant bleeding risk.</td>
<td></td>
</tr>
<tr>
<td>- Higher platelet counts (≥ 50,000/mm³ (5 x 10⁹/L) for emergency surgery or invasive procedures.</td>
<td></td>
</tr>
</tbody>
</table>

Methylcaine of sepsis-induced acute lung injury (ALI)/ARDS

| Target a tidal volume of 6 ml/kg (predicted body weight) in patients with ALI/ARDS. | |
| Target an inspiratory peak pressure < 30 cm H₂O or H₂O pressure corrected for changes in airway pressure when assessing plateau pressure. | |
| Allow PEEP to increase above normal if needed to minimize platelet pressures and tidal volumes. | |
| Positive end-expiratory pressure (PEEP) should be set to avoid excessive lung collapse at end expiration. | |
| Consider the use of PEEP for ARDS patients requiring potentially injurious levels of FIO₂ or PEEP, provided they are not at risk from positional changes. | |
| Maintain mechanically ventilated patients in a semi-recumbent position (head of the bed raised at 45°) unless contraindicated between 30°–55°. | |
| Non-invasive ventilation may be considered in the minority of ALI/ARDS patients with mild/moderate hypercapnic respiratory failure. | |
| The patients need to be hemodynamically stable, comfortable, easily aruousable, able to protect/clear their airway and expected to recover rapidly. | |

Table 6 Non-invasive ventilation for patients with established ALI who do not have evidence of tissue hypoperfusion. | |

Sedation, analgesia, and neuromuscular blockade in sepsis

| Use sedation protocols with sedation goals for critically ill mechanically ventilated patients. | |
| Use either intermittent bolus sedation or continuous infusion sedation to predetermine end points (sedation scales), with daily interruption/limpitude to promote awakening. Re-titrated if necessary. | |
| Avoid neuromuscular blockers (NMBs) where possible. Monitor depth of sleep with a device of true 30% of time using continuous infusion. | |
| Glucose control | Use IV insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU. | |
| Blood glucose levels should be maintained between 80-120 mg/dL or 4.4-6.7 mmol/L. | |
| CVVH offers easier management in hemodynamically unstable patients. | |
| Bicarbonate therapy | Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidosis with pH ≤ 7.15. | |
| Deep venous thrombosis (DVT) prophylaxis | Use either low-dose unfractionated heparin (UFH) or low-molecular weight heparin (LMWH), unless contraindicated. | |
| Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated. | |
| Use a combination of pharmacological and mechanical therapy for patients who are at very high risk for DVT. | |
| In patients at very high risk LMWH should be used rather than UFH. | |
| Stress ulcer prophylaxis | Provide stress ulcer prophylaxis using H2 blocker or proton pump inhibitor. Benefits of prevention of upper GI bleed must be weighed against the potential for development of ventilator-associated pneumonia. | |
| Consideration for limitation of support | Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations. |
Surviving sepsis in 18 Steps

• Initial resuscitation (first 6 hours)
• Diagnosis
• Antibiotic therapy
• Source identification and control
• Fluid therapy
• Vasopressors (17/10/2011)
• Inotropic therapy (17/10/2011)
• Steroids
• Recombinant human activated protein C

• Blood product administration (18/7/2011)
• Mechanical ventilation of sepsis induced ALI/ARDS
• Sedation, analgesia and neuromuscular blockade (3/10/2011)
• Glucose control
• Renal replacement (7/2/2011)
• Bicarbonate therapy
• DVT prophylaxis
• Stress ulcer prophylaxis
• Consideration for limitation of support
Initial resuscitation (first 6 hours)

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4mmol/l; do not delay pending ICU admission. (1C)
- Resuscitation goals: (1C)
  - Central venous pressure (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 O2 saturation target not achieved: (2C)
  - consider further fluid
  - transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  - dobutamine infusion max 20 μg.kg-1.min-1
- A higher target CVP of 12–15 mmHg is recommended in the presence of mechanical ventilation or pre-existing decreased ventricular compliance.
Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and ScvO₂ central venous oxygen saturation.
Some interesting concepts in early goal directed resuscitation

- Early, how early, how long?
- $\text{SvO}_2$ vs $\text{ScvO}_2$
- Disordered mitochondrial activity
- Ventricular filling pressures vs volumes
  - A matter of compliance?
  - Tricuspid and mitral insufficiency / PHT
- Fluid resuscitation targeted to
  - Flow: esophageal doppler monitoring
  - Microcirculation (gastric tonometry – tissue oxygen monitoring probes)

"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."
Diagnosis

• Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration. *(1C)*
  
  – Obtain **two** or more blood cultures (BCs)
  – One or more BCs should be percutaneous
  – One BC from each vascular access device in place > 48h
  – At least 10 ml per culture tube
  – Culture other sites as clinically indicated

• **Delayed time till positivity**

• Perform imaging studies promptly in order 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 optimise efficacy, prevent resistance, avoid toxicity & minimise costs. (1C)

- Consider combination therapy in Pseudomonas infections. (2D)
- Consider combination empiric therapy in neutropenic patients. (2D)
- Combination therapy no more than 3–5 days and deescalation following susceptibilities. (2D)

- Duration of therapy typically limited to 7–10 days; longer if response slow, undrainable foci of infection, or immunologic deficiencies. (1D)
- Stop antimicrobial therapy if cause is found to be non-infectious. (1D)
Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. Black bars represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The gray bars represent the cumulative fraction of patients having received effective antimicrobials at any given time point.
Source identification and control

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

The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6\% hydroxyethyl starch (130/0.4) compared to 0.9\% sodium chloride (saline) in intensive care patients on mortality

Abstract  Purpose: The intravenous fluid 6\% hydroxyethyl starch (130/0.4) (6\% HES 130/0.4) is used widely for resuscitation but there is limited information on its efficacy and safety. A large-scale multi-centre randomised controlled trial (CHEST) in critically ill patients is currently underway comparing fluid resuscitation with 6\% HES 130/0.4 to 0.9\% sodium chloride on 90-day mortality and other clinically relevant outcomes including renal injury. This report describes the study protocol. Methods: CHEST will recruit 7,000 patients to concealed, random, parallel assignment of either 6\% HES 130/0.4 or 0.9\% sodium chloride for all fluid resuscitation needs whilst in the intensive care unit (ICU). The primary outcome will be all-cause mortality at 90 days post-randomisation. Secondary outcomes will include incident renal injury, other organ failures, ICU and hospital mortality, length of ICU stay, quality of life at 6 months, health economic analyses and in patients with traumatic brain injury, functional outcome. Subgroup analyses will be conducted in four predefined subgroups. All analyses will be conducted on an intention-to-treat basis. Results and conclusions: The study run-in phase has been completed and the main trial commenced in April 2010. CHEST should generate results that will inform and influence prescribing of this commonly used resuscitation fluid.

Keywords Hydroxyethyl starch · Fluid therapy · Resuscitation · Colloids · Randomised controlled trials
Fluid therapy

• Fluid-resuscitate using crystalloids or colloids. (1B)
• Target a CVP of ≥8mmHg (≥12mmHg if mechanically ventilated). (1C)
• Use a fluid challenge technique while associated with a haemodynamic improvement. (1D)
• Give fluid challenges of 1000 ml of crystalloids or 300–500 ml of colloids over 30min. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion. (1D)
• Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement. (1D)
Mechanical ventilation of sepsis induced ALI/ARDS
Glucose control

• Use IV insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU. (1B)
• Aim to keep blood glucose < 150 mg/dl (8.3 mmol/L) using a validated protocol for insulin dose adjustment. (2C)
• Provide a glucose calorie source and monitor blood glucose values every 1–2 hrs (4 hrs when stable) in patients receiving intravenous insulin. (1C)
• Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values. (1B)

Bicarbonate therapy

• Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH ≥ 7.15. (1B)

• 2 Studies: No difference in
  – Hemodynamic variables
  – Vasopressor requirements

• No studies on outcome!
Consideration for limitation of support

We recommend that advance care planning, including the communication of likely outcomes and realistic goals of treatment, be discussed with patients and families (Grade 1D).
Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: Results of a three-year follow-up quasi-experimental study

Álvaro Castellanos-Ortega, MD, PhD; Borja Suberviola, MD; Luis A. García-Astudillo, MD; María S. Holanda, MD; Fernando Ortiz, MD; Javier Llorca, MD, PhD; Miguel Delgado-Rodriguez, MD, MPH, PhD

Objectives: To describe the effectiveness of the Surviving Sepsis Campaign bundles with regard to both implementation and outcome in patients with septic shock and to determine the contribution of the various elements of the bundles to the outcome.

Design: Quasi-experimental study with a historical comparison group.

Setting: The three medical-surgical intensive care units of an academic tertiary care center.

Patients: A total of 384 adult patients in septic shock were enrolled after the educational intervention (September 2005–August 2008) and 96 patients in the historical group (June 2004–May 2005).

Intervention: A hospital-wide quality improvement program based on the implementation of the Surviving Sepsis Campaign guidelines performed between June 2005 and August 2005.

Measurements and Results: In-hospital mortality was reduced from 57.3% in the historical group to 37.5% in the intervention group (p = .001). This difference remained significant after controlling for confounding factors (odds ratio, 0.50; 95% confidence interval, 0.28–0.93). The intervention group had also lower length of stay for survivors in the hospital (36.2 ± 34.8 days vs. 41.0 ± 26.3 days; p = .043) and in the intensive care units (8.4 ± 9.8 days vs. 11.0 ± 9.5 days; p = .004). Improvements in survival were related to the number of bundle interventions completed (p for trend < .001). Compliance with six or more interventions of the 6-hr resuscitation bundle was an independent predictor of survival (adjusted odds ratio, 0.30; 95% confidence interval, 0.17–0.53; p < .001). The only single intervention with impact on mortality was the achievement of ScvO₂ ≥70% (adjusted odds ratio, 0.62; 95% confidence interval, 0.38–0.99; p = .048).

Conclusions: The implementation of the Surviving Sepsis Campaign guidelines was associated with a significant decrease in mortality. The benefits depend on the number of interventions accomplished within the time limits. The 6-hr resuscitation bundle showed greater compliance and effectiveness than the 24-hr management bundle. (Crit Care Med 2010; 38:1036–1043)

Keywords: septic shock; Surviving Sepsis Campaign; guidelines; implementation; outcomes; assessment
Does it work?

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis*

Mitchell M. Levy, MD; R. Phillip Dellinger, MD; Sean R. Townsend, MD; Walter T. Linde-Zwirble; John C. Marshall, MD; Julian Bion, MD; Christa Schorr, RN, MSN; Antonio Artigas, MD; Graham Ramsay, MD; Richard Beale, MD; Margaret M. Parker, MD; Herwig Gerlach, MD, PhD; Konrad Reinhart, MD; Eliezer Silva, MD; Maureen Harvey, RN, MPH; Susan Regan, PhD; Derek C. Angus, MD, MPH; on behalf of the Surviving Sepsis Campaign

Objective: The Surviving Sepsis Campaign (SSC or “the Campaign”) developed guidelines for management of severe sepsis and septic shock. A performance improvement initiative targeted changing clinical behavior (process improvement) via bundles based on key SSC guideline recommendations.

Design and Setting: A multifaceted intervention to facilitate compliance with selected guideline recommendations in the intensive care unit, emergency department, and wards of individual hospitals and regional hospital networks was implemented voluntarily in the United States, Europe, and South America. Elements of the guidelines were “bundled” into two sets of targets to be completed within 6 hrs and within 24 hrs. An analysis was conducted on data submitted from January 2005 through March 2008.

Subjects: A total of 15,022 subjects.

Measurements and Main Results: Data from 165 sites were analyzed to determine the compliance with bundle targets and association with hospital mortality. Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 yrs ($p < .0001$). Compliance with the entire management bundle started at 18.4% in the first quarter and increased to 36.1% by the end of 2 yrs ($p = .008$). Compliance with all bundle elements increased significantly, except for inspiratory plateau pressure, which was high at baseline. Unadjusted hospital mortality decreased from 37% to 30.8% over 2 yrs ($p = .001$). The adjusted odds ratio for mortality improved the longer a site was in the Campaign, resulting in an adjusted absolute drop of 0.8% per quarter and 5.4% over 2 yrs (95% confidence interval, 2.5–8.4).

Conclusions: The Campaign was associated with sustained, continuous quality improvement in sepsis care. Although not necessarily cause and effect, a reduction in reported hospital mortality rates was associated with participation. The implications of this study may serve as an impetus for similar improvement efforts. (Crit Care Med 2010; 38:367–374)

Key Words: severe sepsis; septic shock; knowledge transfer; performance measures; Surviving Sepsis Campaign; performance improvement; sepsis bundles; quality improvement
Which bundles?

Table 1. Sepsis bundles definitions and compliance criteria

<table>
<thead>
<tr>
<th>6-hr resuscitation bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serum lactate measured as early as possible from the time of severe sepsis presentation</td>
</tr>
<tr>
<td>2. Obtain blood cultures before antibiotic administration</td>
</tr>
<tr>
<td>3. From the time of severe sepsis presentation, broad-spectrum antibiotics administered within 3 hrs for emergency department admissions and 1 hr for nonemergency department intensive care unit admissions</td>
</tr>
<tr>
<td>In the event of hypotension</td>
</tr>
<tr>
<td>4. Deliver an initial minimum of 500-1000 mL of crystalloid (or colloid equivalent) over a 30-min period</td>
</tr>
<tr>
<td>In the event of persistent hypotension despite fluid resuscitation (septic shock)</td>
</tr>
<tr>
<td>5. Achieve and maintain mean arterial pressure ≥65 mm Hg</td>
</tr>
<tr>
<td>6. Achieve central venous pressure of ≥8 mm Hg</td>
</tr>
<tr>
<td>7. Achieve central venous oxygen saturation of ≥70%</td>
</tr>
<tr>
<td>• Compliance with intervention 1 was considered as having been achieved if it was accomplished within 6 hrs from severe sepsis presentation</td>
</tr>
<tr>
<td>• Compliance with interventions 2 and 3 was considered as having been achieved if they were accomplished within the time limits described from the time of severe sepsis presentation</td>
</tr>
<tr>
<td>• Compliance with interventions 4, 5, 6, and 7 was considered as having been achieved if they were accomplished within 6 hrs from hypotension presentation</td>
</tr>
<tr>
<td>• Compliance with the 6-hr resuscitation bundle was considered as having been achieved if the 7 interventions described in the bundle were accomplished within the specific time limits of each single intervention</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>24-hr management bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Administer intravenous hydrocortisone 300 mg/day for 7 days in 3 divided doses to patients with refractory hypotension despite adequate fluid replacement and vasopressors</td>
</tr>
<tr>
<td>2. Administer protein C activated (drotrecogin alfa) to patients with septic shock, ≥2 sepsis-induced organ failures, and no contraindications</td>
</tr>
<tr>
<td>3. Maintain glucose control greater than lower limit of normal but the median value &lt;150 mg/dL (8.3 mmol/L)</td>
</tr>
<tr>
<td>4. Maintain the median value of inspiratory plateau pressures &lt;30 cm H₂O for mechanically ventilated patients</td>
</tr>
</tbody>
</table>

Compliance with the 24-hr management bundle was considered as having been achieved if the four interventions described in the bundle were obtained during the first 24 hrs from septic shock presentation.
GUIDELINES FOR MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Initial resuscitation (first 6 hours)
- Begin resuscitation immediately in patients with hypotension or elevated serum lactate ≥2mmol/L; do not delay pending ICU admission. (a)
- Resuscitation goals:
  - Central venous pressure (CVP): 8–12 mm Hg
  - Mean arterial pressure ≥65 mm Hg
  - Urine output ≥0.5 mL/kg/hr
  - Central venous (superior vena cava) oxygen saturation ≥70%, or mixed venous ≥60%
- If venous O2 saturation target not achieved:
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit ≥30%
  - Dobutamine infusion max 20 μg/kg·min⁻¹
- A higher target CVP of 12-15 mm Hg is recommended in the presence of mechanical ventilation or pre-existing decreased ventilatory compliance.

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

Antibiotic therapy
- Begin intravenous antibiotics as early as possible, and always within the first hour of recognizing severe sepsis (a) and septic shock. (a)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source. (a)
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, & minimize costs. (a)
- Consider combination therapy in Pseudomonas infections. (a)
- Consider combination empiric therapy in neutropenic patients. (a)
- Combination therapy no more than 3-5 days and de-escalation following susceptibilities. (a)
- Duration of therapy typically limited to 7-10 days; longer if response slow, undrained foci of infection, or immunologic deficiencies. (a)
- Stop antimicrobial therapy if cause is found to be non-infectious. (a)

Source identification and control
- A specific anatomic site of infection should be established as rapidly as possible (a) and within the first 6 hours of presentation. (a)
- Formally evaluate patient for a focus of infection amenable to source control measures (eg: abscess drainage, tissue debridement). (a)
- Implement source control measures as soon as possible following successful initial resuscitation. (a)
- Exception: Infected pancreatic necrosis, where surgical intervention best delayed. (a)
- Choose source control measure with maximum efficacy and minimal physiologic upsets. (a)
- Remove intravascular access devices if potentially infected. (a)

Fluid therapy
- Fluid-resuscitate using crystalloids or colloids. (a)
- Target a CVP of ≥8 mmHg (≥12 mmHg if mechanically ventilated). (a)
- Use a fluid challenge technique while associated with a hemodynamic improvement. (a)
- Give fluid challenges of 1000 mL of crystalloids or 300-500 mL of colloids over 30 minutes. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion. (a)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement. (a)

Vasopressors
- Maintain MAP ≥65 mmHg. (a)
- Norepinephrine or dopamine centrally administered are the initial vasopressors of choice. (a)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor or in septic shock. (a)
- Vasopressin or norepinephrine may be subsequently added to norepinephrine with an intention of an effect equivalent to norepinephrine alone. (a)
- Use epi- or norepinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine. (a)
- Do not use low-dose dopamine for renal protection. (a)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical. (a)

Inotropic therapy
- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output. (a)
- Do not increase cardiac index to predetermined supranormal levels. (a)
Steroids
- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors.
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone.
- Hydrocortisone is preferred to dexamethasone.
- Fludrocortisone (50 μg orally once a day) may be included if an alternative to hydrocortisone is being used which lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used.
- Steroid therapy may be weaned once vaspressors are no longer required.
- Hydrocortisone dose should be ≤500mg/day.
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it.

Recombinant human activated protein C (rhAPC)
- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥ 25 or multiple organ failure) if there are no contraindications.
- Adult patients with severe sepsis and low risk of death (eg: APACHE II ≤ 12 or one organ failure) should not receive rhAPC.

Blood product administration
- Give red blood cells when hemoglobin decreases to ≤17 g/dL (170 g/L) to target a hemoglobin of 7.0 - 9.0 g/dL in adults.
- A higher hemoglobin level may be required in special circumstances (eg: myocardial ischemia, severe hypoxemia, acute hemorrhage, cardiac cyanosis, or lactic acidosis).
- Do not use erythropoietin to treat sepsis-related anemia.
- Erythropoietin may be used for other accepted reasons.
- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures.
- Do not use antithrombin therapy.
- Administer platelets when:
  - counts are ≤150,000/mm³ (≤150 x 10⁹/l) regardless of bleeding
  - counts are ≤50,000/mm³ (≤50 x 10⁹/l) and there is significant bleeding risk.
  - Higher platelet counts (≥350,000/mm³ (≥350 x 10⁹/l)) are typically required for surgery or invasive procedures.

Mechanical ventilation of sepsis-induced acute lung injury (ALI)/ARDS
- Target a tidal volume of 6mL/kg (predicted) body weight in patients with ALI/ARDS.
- Target an initial upper limit plateau pressure ≤30 cmH₂O.
- Consider chest wall compliance when assessing plateau pressure.
- Allow PaCO₂ to increase above normal, if needed, to minimize plateau pressures and tidal volumes.
- Positive end expiratory pressure (PEEP) should be set to avoid excessive lung collapse at end expiration.
- Consider using the prone position for ARDS patients requiring potentially injurious levels of FiO₂ or plateau pressure, provided they are not at risk from positional changes.
- Maintain mechanically ventilated patients in a semi-recumbent position unless contraindicated.
- Suggested target elevation 30 - 45 degrees.
- Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild-moderate hypoxic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly.
- Use a weaning protocol and a spontaneous breathing trial (SBT) regularly to evaluate the potential for discontinuing mechanical ventilation.
- SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H₂O or a T-piece.
- Before the SBT, patients should:
  - be arousable
  - be hemodynamically stable without vasopressors
  - have no new potentially serious conditions
  - have low ventilatory and end-expiratory pressure requirement.
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS.
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion.
- Use antibiotics for patients with established ALI who do not have evidence of tissue hypoperfusion.

Sedation, analgesia, and neuromuscular blockade in sepsis
- Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients.
- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-introduce if necessary.
- Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions.

Glucose control
- Use IV insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU.
- Aim to keep blood glucose 128-180 mg/dL by using a validated protocol for insulin dose adjustment.
- Provide a glucose calorie source and monitor blood glucose values every 1-2 hours (4 hours when stable) in patients receiving intravenous insulin.
- Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values.

Renal replacement
- Intermittent hemodialysis and continuous veno-venous hemofiltration (CVVH) are considered equivalent.
- CVVH offers easier management in hemodynamically unstable patients.

Bicarbonate therapy
- Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH ≤ 7.35.

Deep vein thrombosis (DVT) prophylaxis
- Use either low-dose unfractionated heparin (UHF) or low-molecular weight heparin (LMWH), unless contraindicated.
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated.
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for DVT.
- In patients at very high risk LMWH should be used rather than UHF.

Stress ulcer prophylaxis
- Provide stress ulcer prophylaxis using H₂ blockers or proton pump inhibitor. Benefits of prevention of upper GI bleed must be weighed against the potential for development of ventilator-acquired pneumonia.

Consideration for limitation of support
- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations.

Prepared on behalf of the SSC by Dr Jeremy Willison & Professor Julian Bion
References

References


References

References

- The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee. The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. Intensive Care Med. 2011 Feb 10. [Epub ahead of print]