

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

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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.

Methods: The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UG). Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations.

Results: Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1 C); blood cultures

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this on the journal's Web site (<http://journals.lww.com/ccmjournal>). Complete author and committee disclosures are listed in Supplemental Digital Content 1 (<http://links.lww.com/CCM/A615>).

This article is being simultaneously published in *Critical Care Medicine* and *Intensive Care Medicine*.

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DOI: 10.1097/CCM.0b013e31827e83af

incidence of ventilator-associated pneumonia (VAP); this infection control measure can then be instituted in health-care settings and regions where this methodology is found to be effective (grade 2B).

- 1b. We suggest oral chlorhexidine gluconate (CHG) be used as a form of oropharyngeal decontamination to reduce the risk of VAP in ICU patients with severe sepsis (grade 2B).

Rationale. Careful infection control practices (eg, hand washing, expert nursing care, catheter care, barrier precautions, airway management, elevation of the head of the bed, subglottic suctioning) should be instituted during the care of septic patients as reviewed in the nursing considerations for the Surviving Sepsis Campaign (114). The role of SDD with systemic antimicrobial prophylaxis and its variants (eg, SOD, CHG) has been a contentious issue ever since the concept was first developed more than 30 years ago. The notion of limiting the acquisition of opportunistic, often multidrug-resistant, healthcare-associated microorganisms has its appeal by promoting “colonization resistance” from the resident microbiome existing along mucosal surfaces of the alimentary tract. However, the efficacy of SDD, its safety, propensity to prevent or promote antibiotic resistance, and cost-effectiveness remain debatable despite a number of favorable meta-analyses and controlled clinical trials (115). The data indicate an overall reduction in VAP but no consistent improvement in mortality, except in selected populations in some studies. Most studies do not specifically address the efficacy of SDD in patients who present with sepsis, but some do (116–118).

Oral CHG is relatively easy to administer, decreases risk of nosocomial infection, and reduces the potential concern over promotion of antimicrobial resistance by SDD regimens. This remains a subject of considerable debate, despite the recent evidence that the incidence of antimicrobial resistance does not change appreciably with current SDD regimens (119–121). The grade 2B was designated for both SOD and CHG as it was felt that risk was lower with CHG and the measure better accepted despite less published literature than with SOD.

Supplemental Digital Content 3 (<http://links.lww.com/CCM/A615>) shows a GRADEpro Summary of Evidence Table for the use of topical digestive tract antibiotics and CHG for prophylaxis against VAP.

Hemodynamic Support and Adjunctive Therapy (Table 6)

G. Fluid Therapy of Severe Sepsis

1. We recommend crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B). (This recommendation is based on the results of the VISEP [128], CRYSTMAS [122], 6S [123], and CHEST [124] trials. The results of the recently completed CRYSTAL trial were not considered.)

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

Rationale. The absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions, together with the expense associated with colloid solutions, supports a high-grade recommendation for the use of crystalloid solutions in the initial resuscitation of patients with severe sepsis and septic shock.

Three recent multicenter RCTs evaluating 6% HES 130/0.4 solutions (tetra starches) have been published. The CRYSTMAS study demonstrated no difference in mortality with HES vs. 0.9% normal saline (31% vs. 25.3%, $p = 0.37$) in the resuscitation of septic shock patients; however the study was underpowered to detect the 6% difference in absolute mortality observed (122). In a sicker patient cohort, a Scandinavian multicenter study in septic patients (6S Trial Group) showed increased mortality rates with 6% HES 130/0.42 fluid resuscitation compared to Ringer's acetate (51% vs. 43% $p = 0.03$) (123). The CHEST study, conducted in a heterogeneous population of patients admitted to intensive care (HES vs. isotonic saline, $n = 7000$ critically ill patients), showed no difference in 90-day mortality between resuscitation with 6% HES with a molecular weight of 130 kD/0.40 and isotonic saline (18% vs. 17%, $p = 0.26$); the need for renal replacement therapy was higher in the HES group (7.0% vs. 5.8%; relative risk [RR], 1.21; 95% confidence interval [CI], 1.00–1.45; $p = 0.04$) (124). A meta-analysis of 56 randomized trials found no overall difference in mortality between crystalloids and artificial colloids (modified gelatins, HES, dextran) when used for initial fluid resuscitation (125). Information from 3 randomized trials ($n = 704$ patients with severe sepsis/septic shock) did not show survival benefit with use of heta-, hexa-, or pentastarches compared to other fluids (RR, 1.15; 95% CI, 0.95–1.39; random effect; $I^2 = 0\%$) (126–128). However, these solutions increased the risk of acute kidney injury (RR, 1.60; 95% CI, 1.26–2.04; $I^2 = 0\%$) (126–128). The evidence of harm observed in the 6S and CHEST studies and the meta-analysis supports a high-level recommendation advising against the use of HES solutions in patients with severe sepsis and septic shock, particularly since other options for fluid resuscitation exist. The CRYSTAL trial, another large prospective clinical trial comparing crystalloids and colloids, was recently completed and will provide additional insight into HES fluid resuscitation.

The SAFE study indicated that albumin administration was safe and equally as effective as 0.9% saline (129). A meta-analysis aggregated data from 17 randomized trials ($n = 1977$) of albumin vs. other fluid solutions in patients with severe sepsis/septic shock (130); 279 deaths occurred among 961 albumin-treated patients vs. 343 deaths among 1,016 patients treated with other fluids, thus favoring albumin (odds ratio [OR], 0.82; 95% CI, 0.67–1.00; $I^2 = 0\%$). When albumin-treated patients were compared

TABLE 6. Recommendations: Hemodynamic Support and Adjunctive Therapy**G. Fluid Therapy of Severe Sepsis**

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic Therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min 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 MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. 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 (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

with those receiving crystalloids (seven trials, $n = 1441$), the OR of dying was significantly reduced for albumin-treated patients (OR, 0.78; 95% CI, 0.62–0.99; $I^2 = 0\%$). A multi-center randomized trial ($n = 794$) in patients with septic shock compared intravenous albumin (20 g, 20%) every 8 hrs for 3 days to intravenous saline solution (130); albumin therapy was associated with 2.2% absolute

reduction in 28-day mortality (from 26.3% to 24.1%), but did not achieve statistical significance. These data support a low-level recommendation regarding the use of albumin in patients with sepsis and septic shock (personal communication from J.P. Mira and as presented at the 32nd International SICEM Congress 2012, Brussels and the 25th ESICM Annual Congress 2012, Lisbon).

4. We recommend an initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (see Initial Resuscitation recommendations) (grade 1C).
5. We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

Rationale. Dynamic tests to assess patients' responsiveness to fluid replacement have become very popular in recent years in the ICU (131). These tests are based on monitoring changes in stroke volume during mechanical ventilation or after passive leg raising in spontaneously breathing patients. A systematic review (29 trials, $n = 685$ critically ill patients) looked at the association between stroke volume variation, pulse pressure variation, and/or stroke volume variation and the change in stroke volume/cardiac index after a fluid or positive end-expiratory pressure challenge (132). The diagnostic OR of fluid responsiveness was 59.86 (14 trials, 95% CI, 23.88–150.05) and 27.34 (five trials, 95% CI, 3.46–55.53) for the pulse pressure variation and the stroke volume variation, respectively. Utility of pulse pressure variation and stroke volume variation is limited in the presence of atrial fibrillation, spontaneous breathing, and low pressure support breathing. These techniques generally require sedation.

H. Vasopressors

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

Rationale. Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a threshold MAP, autoregulation in critical vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow (133, 134). The titration of norepinephrine to a MAP as low as 65 mm Hg has been shown to preserve tissue perfusion (134). Note that the consensus definition of sepsis-induced hypotension for use of MAP in the diagnosis of severe sepsis is different (MAP < 70 mm Hg) from the evidence-based target of 65 mm Hg used in this recommendation. In any case, the optimal MAP should be individualized as it may be higher in patients with atherosclerosis and/or previous hypertension than in young patients without cardiovascular comorbidity. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension; in a young, previously normotensive patient, a lower MAP might be adequate. Supplementing endpoints, such as blood pressure, with assessment of regional and global perfusion, such as blood lactate concentrations, skin perfusion, mental status, and urine output, is important. Adequate fluid resuscitation

is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used; however, using vasopressors early as an emergency measure in patients with severe shock is frequently necessary, as when diastolic blood pressure is too low. When that occurs, great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

2. We recommend norepinephrine as the first-choice vasopressor (grade 1B).
3. We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to target or decreasing norepinephrine dosage (UG).
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03–0.04 U/min should be reserved for salvage therapy (failure to achieve an adequate MAP with other vasopressor agents) (UG).
6. We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in the following circumstances: (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve the MAP target (grade 1C).

Rationale. The physiologic effects of vasopressor and combined inotrope/vasopressors selection in septic shock are set out in an extensive number of literature entries (135–147). **Table 7** depicts a GRADEpro Summary of Evidence Table comparing dopamine and norepinephrine in the treatment of septic shock. Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine (148). It may also influence the endocrine response via the hypothalamic pituitary axis and have immunosuppressive effects. However, information from five randomized trials ($n = 1993$ patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock (136, 149–152). Indeed, the relative risk of short-term mortality was 0.91 (95% CI, 0.84–1.00; fixed effect; $I^2 = 0\%$) in favor of norepinephrine. A recent meta-analysis showed dopamine was associated with an increased risk (RR, 1.10 [1.01–1.20]; $p = 0.035$); in the two trials that reported