The Surviving Sepsis Campaign Guidelines 2012: Update for Emergency Physicians

Alan E. Jones, MD; Michael A. Puskarich, MD

The Surviving Sepsis Campaign recently developed and published an updated version in 2012 of the international guidelines for the assessment and management of severe sepsis and septic shock. These guidelines reflect literature published in the last 5 years, and many of the recommendations have direct implications for emergency physicians. In this review, we present a concise summary of these recommendations, with a particular focus on those that have changed and those that have direct relevance to the clinical practice of emergency medicine. [Ann Emerg Med. 2014;63:35-47.]

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INTRODUCTION

The Surviving Sepsis Campaign has attempted to increase awareness and establish practice guidelines to improve the recognition and treatment of patients with severe sepsis and septic shock. Since the publication of the last iteration of the guidelines in 2008,1 several studies with major implications to the initial assessment and management of the emergency department (ED) patient with severe sepsis and septic shock have been published. The results of these studies were incorporated into the newly published 2012 Surviving Sepsis Campaign Guidelines,2 which has been endorsed by numerous stakeholders from the fields of critical care, infectious diseases, and nursing and by the American College of Emergency Physicians and the Society for Academic Emergency Medicine. The goal of this review is to provide the emergency practitioner a synopsis of the recent changes in guidelines, with a particular emphasis on those that may have direct implications for ED assessment and management of early sepsis. This article will also provide a brief discussion of the various studies that led to these changes in recommendations so that the reader may have a better understanding of the current state of the art and relevant gaps in the literature.

DEFINITIONS AND WEIGHTING OF THE EVIDENCE

Definitions of sepsis and its variants are based on consensus definitions.3 Sepsis is defined as probable (documented or suspected) infection and signs of systemic inflammation. Severe sepsis is defined as sepsis and organ dysfunction or tissue hypoperfusion (Figure 1). Septic shock is defined as sepsis-induced hypotension despite adequate fluid resuscitation.

Evidence incorporated in the guidelines was evaluated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as follows: grade 1 (strong) and grade 2 (weak) recommendations are based on the committee’s overall assessment of the risks and benefits of the intervention, which is of greater importance to clinicians than the quality of evidence. Grade 1 guidelines use the language “we recommend,” whereas the weaker grade 2 guidelines carry the language “we suggest.” Considerations in grading evidence included quality, certainty about the balance of risks and harms, certainly in value, and resource implications. Quality of evidence was classified as high (A), moderate (B), low (C), or very low (D). High-quality randomized controlled trials represent class A, whereas downgraded randomized controlled trials because of methodological issues or upgraded observational studies are representative of class B. Well-done observational studies typically represent class C, whereas downgraded studies or expert opinion represent class D.

SPECIFIC GUIDELINE RECOMMENDATIONS OF RELEVANCE TO EMERGENCY PHYSICIANS

The primary goal of this review is to provide a summary of both the changes to the Surviving Sepsis Campaign Guidelines and those of foremost relevance to emergency medicine. These changes are summarized in the Table and are discussed in further detail throughout the review.

In this version of the guidelines, the Surviving Sepsis Campaign has issued a general statement that the recommendations are considered best practices but do not represent standard of care to which physicians should be held. As stated in the guidelines, “Thus, these recommendations are intended to be best practice (the committee considers this a goal for clinical practice) and not created to represent standard of care.” This is important inasmuch as, in previous versions of the guidelines, there were instances in which certain specific recommendations were stated to not represent standard of care (eg, time to antibiotics); however, in this version this statement applies to all the recommendation contained in the guidelines. Also, there continue to be some internal inconsistencies in the document most significantly related to...
recommendations of resuscitation that will be addressed in detail in the following commentary.

**SCREENING AND PRACTICE 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).

**SEVERE SEPSIS: SEPSIS-INDUCED TISSUE HYPOPERFUSION OR ORGAN DYSFUNCTION (ANY OF THE FOLLOWING THOUGHT TO BE DUE TO INFECTION)**

Sepsis-induced hypotension

Lactate level above upper limits of laboratory normal levels

Urine output <0.5 mL/kg per hour for more than 2 h despite adequate fluid resuscitation

Acute lung injury with PaO₂/FiO₂ <250 in the absence of pneumonia as infection source

Acute lung injury with PaO₂/FiO₂ <200 in the presence of pneumonia as infection source

Creatinine level >2.0 mg/dL

Bilirubin level >2 mg/dL

Platelet count <100,000 μL

Coagulopathy (INR >1.5)

**SBP**, Systolic blood pressure; **MAP**, mean arterial pressure; **INR**, international normalized ratio; **aPTT**, activated partial thromboplastin time.

Performance improvement efforts in severe sepsis should be used to improve patient outcomes (ungraded).

Data suggest that early recognition of sepsis and initiation of appropriate interventions improves patient-centered outcomes. Numerous trials have demonstrated significant reductions in mortality after initiation of early care for the treatment of severe sepsis. Furthermore, the reduction in mortality found after the implementation of sepsis screening tools in the ICU suggests that...
<table>
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<th>Recommendation</th>
<th>2008 Guidelines</th>
<th>2012 Guidelines</th>
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<tr>
<td>Screening and practice improvement</td>
<td>None</td>
<td>Routinely screen potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C)</td>
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<tr>
<td></td>
<td>Fluid-resuscitate with crystalloids or colloids (1B)</td>
<td>Implement hospital-based performance improvement efforts in severe sepsis (UG)</td>
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<td>Target a CVP of $&gt;8$ mm Hg ($&gt;12$ mm Hg if mechanically ventilated) (1C)</td>
<td>Give crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B)</td>
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<td>Use a fluid challenge technique while associated with a hemodynamic improvement (1D)</td>
<td>Do not use hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B)</td>
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<td>Give fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids during 30 min. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)</td>
<td>Give albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C)</td>
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<td>Reduce the rate of fluid administration if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)</td>
<td>Administer 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 (grade 1C).</td>
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<td></td>
<td>Antimicrobial therapy</td>
<td>A fluid challenge technique may 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, pulse rate) variables (UG)</td>
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<td>Begin intravenous antibiotics as early as possible and always within the first hour of recognition of severe sepsis (1D) and septic shock (1B)</td>
<td>Administer effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C)</td>
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<td>Use broad-spectrum antibiotics: 1 or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)</td>
<td>Choose initial empiric anti-infective therapy of 1 or more drugs that have activity against all likely pathogens (bacterial or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B)</td>
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<td>Consider combination therapy in Pseudomonas infections (2D)</td>
<td>Use combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum $\beta$-lactam and either an aminoglycoside or a fluoroquinolone is for P aeruginosa bacteremia (grade 2B). A combination of $\beta$-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections (grade 2B). Initiate antiviral therapy as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C)</td>
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<td>Consider combination empiric therapy in neutropenic patients (2D)</td>
<td>Avoid the use of antimicrobial agents for patients with severe inflammatory states determined to be of noninfectious cause (UG)</td>
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<td>Stop antimicrobial therapy if cause is found to be noninfectious (1D)</td>
<td>Use protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration $&gt;4$ mmol/L). Goals during the first 6 h of resuscitation:</td>
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<tr>
<td>Resuscitation goals</td>
<td>Begin resuscitation immediately in patients with hypotension or elevated serum lactate $&gt;4$ mmol/L; do not delay pending ICU admission (1C)</td>
<td>CVP 8–12 mm Hg</td>
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<td></td>
<td>Resuscitation goals (1C)</td>
<td>MAP $&gt;65$ mm Hg</td>
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<td></td>
<td>CVP 8–12 mm Hg</td>
<td>Urine output $&gt;0.5$ mL/kg per hour</td>
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<td>MAP $&gt;65$ mm Hg</td>
<td>SvO$_2$ or mixed SvO$_2$ 70% or 65%, respectively</td>
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<td>If venous oxygen saturation target is not achieved (2C)</td>
<td>a) consider further fluid</td>
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<td>b) transfuse packed RBCs if required to hematocrit of $&gt;30%$ or start dobutamine infusion</td>
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<td>In patients with elevated lactate levels, target resuscitation to normalize lactate as rapidly as possible (grade 2C)</td>
</tr>
<tr>
<td>Recommendation</td>
<td>2008 Guidelines</td>
<td>2012 Guidelines</td>
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<td>Vasopressors</td>
<td>Use vasopressor therapy initially to target a MAP of 65 mm Hg (grade 1C)</td>
<td>Use norepinephrine as the first-choice vasopressor (grade 1B)</td>
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<td>Use norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)</td>
<td>Consider administration of epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B)</td>
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<td>Norepinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 U/min may be subsequently added to norepinephrine, with anticipation of an effect equivalent to that of norepinephrine alone.</td>
<td>Consider addition of vasopressin 0.03 U/min to norepinephrine with intent of either increasing MAP or decreasing norepinephrine dosage (UG)</td>
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<td>Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B)</td>
<td>Avoid low-dose vasopressin as the single initial vasopressor for treatment of sepsis-induced hypotension</td>
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<td>Do not use low-dose dopamine for renal protection (1A)</td>
<td>Reserve vasopressin doses higher than 0.03–0.04 U/min for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG)</td>
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<td>For patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)</td>
<td>Select 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)</td>
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<td>Inotropic therapy Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)</td>
<td>Do not use phenylephrine in the treatment of septic shock except in circumstances in which (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)</td>
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<td>Do not increase cardiac index to predetermined supranormal levels (1B)</td>
<td>Do not use low-dose dopamine for renal protection (grade 1A)</td>
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<td>Blood products Give RBCs when hemoglobin decreases to &lt;7.0 g/dL to target a hemoglobin of 7.0–9.0 g/dL in adults (1B). A higher hemoglobin level may be required in special circumstances (eg, myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, lactic acidosis).</td>
<td>Place an arterial catheter in all patients requiring vasopressors as soon as practical if resources are available (UG)</td>
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<td>Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons (1B).</td>
<td>Consider a trial of dobutamine infusion up to 20 μg/kg per minute 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)</td>
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<td>Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (2D)</td>
<td>Do not use inotropes as a strategy to increase cardiac index to predetermined supranormal levels (grade 1B)</td>
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<td>Do not use antithrombin therapy (1B)</td>
<td>Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, transfuse RBCs only when hemoglobin concentration decreases to &lt;7.0 g/dL to target a hemoglobin concentration of 7.0–9.0 g/dL in adults (grade 1B)</td>
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<td>Administer platelets when (2D)</td>
<td>Do not use antithrombin for the treatment of severe sepsis and septic shock (grade 1B)</td>
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<td>Counts are &lt;5,000/mm³ regardless of bleeding; counts are 5,000–30,000/mm³ and there is significant bleeding risk; higher platelet counts (≥50,000/mm³) are required for surgery or invasive procedures</td>
<td>Do not use fresh frozen plasma to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D)</td>
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<td>Administer platelets (2D)</td>
<td>Do not use antithrombin for the treatment of severe sepsis and septic shock (grade 1B)</td>
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<tr>
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<td>In patients with severe sepsis, administer platelets prophylactically when counts are &lt;10,000/mm³ in the absence of apparent bleeding. We suggest prophylactic platelet transfusion 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).</td>
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Corticosteroids

Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly 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 (50 mg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone if 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 adult septic shock unless the patient’s endocrine or corticosteroid history warrants it (1D).

A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 h of presentation (1D).

Formally evaluate patient for a focus of infection amenable to source control measures (eg, abscess drainage, tissue debridement) (1C).

Implement source control measures as soon as possible after successful initial resuscitation (1C) (exception: infected pancreatic necrosis, in which 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).

Source control

Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B).

Allow PaCO₂ to increase above normal, if needed, to minimize plateau pressures and tidal volumes (1C).

Set PEEP to avoid extensive lung collapse at end expiration (1C).

Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45 degrees) unless contraindicated (1B), between 30 and 45 degrees (2C).

Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild to moderate hypoxemic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly (2B).

Blood glucose control

Use intravenous insulin to control hyperglycemia in patients with severe sepsis after stabilization in the ICU (1B).

Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) with a validated protocol for insulin dose adjustment (2C).

Provide a glucose calorie source and monitor blood glucose values every 1–2 h (4 h when stable) for patients receiving intravenous insulin (1C).

Interpret with caution low glucose levels obtained with point-of-care testing because these techniques may overestimate arterial blood or plasma glucose values (1B).

Do not use 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).

Do not use the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).

In treated patients, taper hydrocortisone when vasopressors are no longer required (grade 2D).

Do not administer corticosteroids for the treatment of sepsis in the absence of shock (grade 1D).

When hydrocortisone is administered, use continuous flow (grade 2D).

Consider and exclude specific anatomic diagnoses of infection requiring emergency source control as rapidly as possible, and intervene for source control within the first 12 h after the diagnosis is made, if feasible (grade 1C).

When infected peripancreatic necrosis is identified as a potential source of infection, delay definitive intervention until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

When source control in a severely septic patient is required, use the effective intervention associated with the least physiologic insult (eg, percutaneous rather than surgical drainage of an abscess) (UG).

If intravascular access devices are a possible source of severe sepsis or septic shock, remove them promptly after other vascular access has been established (UG).

Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs 12 mL/kg).

Apply PEEP to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).

Use strategies based on higher rather than lower levels of PEEP for patients with sepsis-induced moderate or severe ARDS (grade 2C).

Elevate the head of the bed elevated to 30–45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia in mechanically ventilated sepsis patients (grade 1B).

Use NIV in that minority of sepsis-induced ARDS patients for whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).

Use a protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose <180 mg/dL rather than an upper target blood glucose <110 mg/dL (grade 1A).

Monitor blood glucose values every 1–2 h until glucose values and insulin infusion rates are stable and then every 4 h thereafter (grade 1C).

Interpret glucose levels obtained with point-of-care testing of capillary blood with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (UG).
time to sepsis recognition is causally related to outcome. However, the guidelines do not cite any specific ED-based screening studies.

The specific addition of recommendations to initiate process improvement programs for sepsis is new to the 2012 guidelines. Such programs can be used to help track efficacy of screening and may assist with the initial choice of effective antimicrobial agents (see "Blood Cultures and Antibiotics" below), as well as compliance with the Surviving Sepsis Campaign Care Bundle (see below).

**FLUID THERAPY**

We recommend that crystalloids be used as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

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

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).

We recommend an initial fluid challenge in patients with sepsis-induced hypoperfusion with suspicion of hypovolemia to achieve a minimum of crystalloids at 30 mL/kg (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).

We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement based on either dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, pulse rate) variables (ungraded).

Several changes in regard to fluid resuscitation that may have direct implications for ED care are included in the 2012 guidelines. Randomized trials have failed to demonstrate any clear benefit of colloids over crystalloids, and given the additional expense of colloids, crystalloids remain recommended as the initial fluid therapy of choice for volume expansion. The suggestion to consider albumin as a recommended therapy for volume expansion in patients requiring large volumes of crystalloids is new to the guidelines and could be considered by emergency physicians. This recommendation is based on a recent meta-analysis completed by Delaney et al., suggesting benefit of albumin compared with crystalloid, as well as the known adverse effects of a largely positive fluid balance during the first 4 days of ICU admission. However, the determination of what defines substantial volume of fluid remains undefined. It therefore is unclear from the guidelines at what volume of fluid physicians should shift from crystalloid- to albumin-based volume resuscitation. Recent concerns about the safety of synthetic colloids, specifically hydroxyethyl starch use associated with an increased incidence of renal failure, has revealed that it is inappropriate to analyze the treatment effect of albumin in aggregate with synthetic colloids, given their different safety profiles.

Because most patients presenting with sepsis have intravascular volume depletion, an empiric fluid bolus for any
patient with suspected severe sepsis with hypotension or an elevated lactate level greater than or equal to 4 mmol/L is recommended. The guidelines do not provide any rationale for the choice of an initial 30 mL/kg crystalloid bolus. This is the point of another internal inconsistency in the document, in which 30 mL/kg crystalloid bolus in the setting of sepsis-induced hypoperfusion with suspicion of hypovolemia is recommended in the fluid therapy section of the actual guidelines; however, the care bundle simply recommends the 30 mL/kg crystalloid bolus in the setting of sepsis-induced hypoperfusion, with no mention of suspicion of hypovolemia. Likewise, the resuscitation goals section recommendations of achievement of parameters related to volume status (central venous pressure and urine output) are based on only identification of sepsis-induced hypoperfusion, with no mention of suspicion of hypovolemia.

Measurement of central venous pressure has been moved from this section but is still recommended as part of the resuscitation goals. The 2012 guidelines now recommend additional measures of volume responsiveness apart from central venous pressure, including static variables, such as arterial pressure and pulse rate, as well as dynamic variables, such as change in pulse pressure or stroke volume variation. This remains an ungraded recommendation, and barring any specific evidence, the choice of method of assessment of fluid response to boluses is left to the treating physician.

**BLOOD CULTURES AND ANTIBIOTICS**

We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in the start of antimicrobial administration (grade 1C). To optimize identification of causative organisms, we recommend obtaining at least 2 sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least 1 obtained percutaneously and 1 through each vascular access device, unless the device was recently (<48 hours) inserted. These blood cultures can be obtained at the same time if they are from different sites. Cultures of other sites (preferably quantitative when appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection, should also be obtained before antimicrobial therapy if doing so does not cause significant delay in antibiotic administration (grade 1C).

The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) should be the goal of therapy.

Remark: Although the weight of the evidence supports prompt administration of antibiotics after the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated.

We recommend that initial empiric anti-infective therapy include 1 or more drugs that have activity against all likely pathogens (bacterial or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens according to each patient’s presenting illness and local patterns of infection. We suggest combination therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as Acinetobacter and Pseudomonas spp (grade 2B). For selected patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum β-lactam and either an aminoglycoside or a fluoroquinolone is suggested for P aeruginosa bacteremia (grade 2B). Similarly, a more complex combination of β-lactam and a macrolide is suggested for patients with septic shock from bacteremic Streptococcus pneumoniae infections (grade 2B).

We suggest that antiviral therapy be initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

We recommend that antimicrobial agents not be used in patients with severe inflammatory states determined to be of noninfectious cause (ungraded).

Several changes to the guidelines of importance to emergency physicians are present in this version of the guidelines. The major messages about antimicrobials are to obtain blood cultures immediately after recognition of severe sepsis, to administer broad-spectrum antimicrobials as soon as feasible, and to treat for all possible organisms, including fungi and viruses should risk factors be present. Because the de-escalation of broad-spectrum antibiotics is critical for the minimization of antibiotic toxicity, cost, and the development of antibiotic resistance, obtaining at least 2 sets of blood cultures before the initiation of antibiotics is recommended.

Given the importance placed on timing of antimicrobials, as well as the aforementioned importance of cultures, weighing these 2 competing interests has led to the recommendation that broad-spectrum antibiotics be administered before blood cultures are obtained if those cultures are expected to take longer than 45 minutes to obtain. Retrospective observational data suggest that timing of antibiotic administration from the onset of hypotension may be a determinant of patient outcome in severe sepsis and septic shock, and these current recommendations suggest administration of broad-spectrum antibiotics for all potential pathogens (including viral and fungal organisms) within 1 hour of the recognition of shock. However, the issue of timing of antibiotic administration is exceptionally complex, as acknowledged by the guidelines through the insertion of the following remark: “Although the weight of the evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated.”

Timing of antibiotic administration is another area of internal inconsistency in the document. The guidelines recommend administration within 1 hour of severe sepsis and septic shock recognition; however, the care bundle goal is administration of antibiotics within 3 hours of ED triage. This point is exceedingly important for clinicians, and both the 2008 and 2012 guidelines explicitly state in that these times (within 1 hour of recognition...
or 3 hours of triage) are not the standard of care. The 2012 guidelines go so far as to state that there are no practice data to support the recommendations and recommend further research on optimal antibiotic timing.

Choice of antibiotic therapy should cover all likely pathogens. The guidelines specifically call attention to the increasing prevalence of oxacillin (methicillin)-resistant *Staphylococcus aureus* and Gram-negative bacilli in some communities and health care settings resistant to broad-spectrum β-lactams and carbapenems, and suggest empiric coverage for such organisms in patients from settings in which the prevalence of these organisms is significant. Clinicians should also consider the possibility of fungal infections, particularly in patients with risk factors for candidemia such as immunosuppressed or neutropenic state, previous broad-spectrum antibiotic therapy, or colonization of multiple sites.

Although blood cultures are important for de-escalation decisions, it is critical to note the guidelines’ focus on ensuring initial adequate antibiotic coverage: “Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antimicrobial susceptibilities are defined. Although a global restriction of antibiotics is an important strategy to reduce the development of antimicrobial resistance and to reduce cost, it is not an appropriate strategy in the initial therapy for this patient population.”

The Surviving Sepsis Campaign Guidelines 2012 recommend the protocolized, quantitative resuscitation of severely ill patients with septic shock who are at high risk of death.2 The use of combination therapy carries the additional benefit of being more likely to have at least 1 antibiotic effective against drug-resistant organisms. The development of a standardized set of suggested antibiotics according to risk factors might be a good addition to process improvement strategies recommended by the guidelines (see “Screening and Practice Improvement”).

**RESUSCITATION GOALS**

We recommend the protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as part of a treatment protocol (grade 1C):

- central venous pressure 8 to 12 mm Hg
- mean arterial pressure level greater than or equal to 65 mm Hg
- urine output greater than or equal to 0.5 mL/kg per hour
- ScvO₂ or mixed SvO₂ 70% or 65%, respectively

We suggest targeting resuscitation to normalize lactate levels in patients with elevated lactate levels as a marker of tissue hypoperfusion (grade 2C).

Numerous studies have demonstrated the benefit of early protocolized resuscitation protocols on survival in severe sepsis.5-9,11 Protocolized resuscitation refers to the targeting of specific physiologic parameters in a sequential manner, with the goal of eradicating tissue hypoperfusion and mismatching of oxygen supply and demand that typifies shock states. Of critical importance for emergency physicians is that data from a meta-analysis demonstrate survival benefit when such quantitative resuscitation protocols are initiated early, with no clear benefit conferred if initiated late.12 Therefore, it is prudent to initiate resuscitative measures when severe sepsis is recognized.

The Surviving Sepsis Campaign recommends a tiered resuscitation based on the concepts of first maximizing preload through the use of volume-expanding agents, ensuring adequate organ perfusion to persistently hypotensive patients through the use of vasopressors, monitoring adequate urine output as a surrogate for vital organ perfusion, and finally ensuring oxygen supply and demand matching. The specific goals of the quantitative resuscitation protocol in regard to central venous pressure, mean arterial pressure, urine output, and ScvO₂ or mixed SvO₂ remain unchanged. One addition in this version of the guidelines was the introduction of lactate clearance, with a specific goal of lactate normalization, as a suggested goal of resuscitation. Lactate clearance was evaluated in 2 randomized clinical trials. In the first, a lactate clearance of 10% was found to be noninferior to ScvO₂ as the final goal of an early quantitative resuscitation protocol.23 In the second, the addition of a lactate clearance goal of 20% to traditional goals of early sepsis resuscitation including ScvO₂ led to improved survival in an adjusted analysis.24 These trials used different goals of lactate clearance in the setting of different protocols. Although the Surviving Sepsis Campaign recommends lactate normalization as a goal of resuscitation, no clinical trial data using this goal are yet available, leading to its 2C recommendation.

There are several important inconsistencies in the 2012 guidelines related to resuscitation goals. First, the simple measurement of central venous pressure, ScvO₂, and initial and repeated lactate concentration (if the initial lactate measurement was elevated) is recommended within 6 hours in the care bundle (see “Surviving Sepsis Campaign Care Bundle” below), but the bundle does not require achievement of any particular value of these measurements as it did in the 2008 version. This distinction is important because the actual guidelines recommend that certain values of these parameters be achieved; however, the bundle does not.

Second, the guidelines recommend that the resuscitation goals be achieved within 6 hours of recognition of sepsis-induced hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L); however, completion of the 3- and 6-hour resuscitation components of the bundle start the clock at ED triage. It is unclear exactly how clinicians should reconcile this inconsistency.
VASOPRESSORS

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

We recommend norepinephrine as the first-choice vasopressor (grade 1B).

We suggest epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).

Vasopressin (up to 0.03 U/minute) can be added to norepinephrine with the intent of increasing mean arterial pressure to target or decreasing norepinephrine dosage (ungraded).

Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses higher than 0.03 to 0.04 U/minute should be reserved for salvage therapy (failure to achieve an adequate mean arterial pressure with other vasopressor agents) (ungraded).

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).

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) it is to be used as salvage therapy when combined inotropic/vasopressor drugs and low-dose vasopressin have failed to achieve the mean arterial pressure target (grade 1C).

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

We recommend that all patients requiring vasopressors receive an arterial catheter as soon as practical if resources are available (ungraded).

Major changes in specific recommendations for and against the use of various vasopressors are of particular importance to emergency physicians. The specific goal of a mean arterial pressure of 65 mm Hg remains unchanged, a recommendation based on observational data. A recent large randomized trial comparing dopamine with norepinephrine for the treatment of shock found that dopamine was associated with an increased risk of adverse events, particularly tachydysrhythmias, even though no clear mortality difference between the 2 vasopressors was found overall; however, the study did find that norepinephrine was associated with superior outcomes in the cardiac subgroup.25

A summary of all available evidence included in the 2012 Surviving Sepsis Campaign guidelines, however, suggests that in sepsis patients dopamine is indeed associated with increased rates of not only supraventricular and ventricular tachycardias but also increased short-term mortality compared with norepinephrine.2

Low-dose vasopressin in addition to norepinephrine versus norepinephrine alone demonstrated no difference in mortality the Vasopressin Versus Norepinephrine Infusion in Patients with Septic Shock trial.26 Although ungraded by the guidelines, high-dose vasopressin can be used as an additional vasopressor agent; however, it has been associated with cardiac, splanchnic, and digital ischemic injury,27 which is the basis for the maximum dosage recommendation of 0.03 U/min. Phenylephrine, a pure α-adrenergic agonist, can decrease stroke volume and is therefore not recommended for use in the treatment of septic shock except in very specific clinical circumstances. In light of these data, norepinephrine is recommended as the first-line vasopressor, and other vasopressors are indicated only for specific clinical circumstances summarized above. Recommendations against the use of low-dose dopamine for renal protection remain unchanged, and the use of arterial catheters for monitoring, although recommended, is ungraded because of lack of evidence.

INOTROPIC THERAPY

We recommend that a trial of dobutamine infusion up to 20 µg/kg per minute 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 achievement of adequate intravascular volume and adequate mean arterial pressure (grade 1C).

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

Recommendations about the use of inotropes has been minimally amended in the 2012 Surviving Sepsis Campaign guidelines. Dobutamine is recommended for evidence of cardiac dysfunction, as evidenced by either physiologic measurements of cardiac function (unchanged from the 2008 guidelines) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure. This second indication for dobutamine infusion is new to the guidelines, and evidence of ongoing hypoperfusion could presumably be implied by low ScvO2 or impaired lactate clearance, though this is not stated explicitly in the guidelines. Supraphysiologic driving of oxygen delivery is still recommended against, given previous clinical trial data.

BLOOD PRODUCTS

Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, we recommend that RBC 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).

We recommend not using erythropoietin as a specific treatment of anemia associated with severe sepsis (grade 1B).

We suggest that fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).

We recommend against antithrombin administration for the treatment of severe sepsis and septic shock (grade 1B).

In patients with severe sepsis, we suggest that platelets be administered prophylactically when counts are less than 10,000/mm³ (10×10⁹/L) in the absence of apparent bleeding, as well as when counts are less than 20,000/mm³ (20×10⁹/L) if the patient has a
significant risk of bleeding. Higher platelet counts (≥50,000/mm³ [50 × 10⁹/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

Recommendations about blood product administration remain similar in this version of the guidelines, though the current version clarifies a seemingly contradictory recommendation about blood transfusion thresholds. Specifically, a transfusion threshold of 7.0 g/dL is clarified as the treatment goal after resolution of tissue hypoperfusion. This threshold is derived from data suggesting that in the ICU, patients transfused when the hemoglobin level decreased below 7.0 g/dL to maintain a level between 7.0 and 9.0 g/dL fared no worse than patients transfused when the hemoglobin level decreased below 10.0 g/dL to maintain a level between 7.0 and 9.0 g/dL.28 Therefore, in the absence of extenuating circumstances, such as ongoing ischemia, a tolerance of anemia to a level of 7.0 to 9.0 g/dL is permissible in the fully resuscitated patient. Guidance against erythropoietin, antithrombin, and fresh frozen plasma in the absence of bleeding or planned intervention remains unchanged. Data about the use of platelet transfusion are sparse and based primarily on expert opinion. In the absence of bleeding, platelet transfusion is not recommended except for cases in which the platelet count is less than 10 × 10⁹/L (increased from <5 × 10⁹/L in the 2008 guidelines), which increases to less than 20 × 10⁹/L when the patient is at high risk of bleeding and less than 50 × 10⁹/L when the patient is actively bleeding or has a planned invasive procedure.

CORTICOSTEROIDS

We suggest not using intravenous hydrocortisone as a treatment of adult patients with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg/day (grade 2C).

We suggest not using the adrenocorticotropic hormone (ACTH) stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).

We suggest that clinicians taper the treated patient from steroid therapy when vasopressors are no longer required (grade 2D).

We recommend that corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).

When low-dose hydrocortisone is administered, we suggest using continuous infusion rather than repetitive bolus injections (grade 2D).

The primary change of specific relevance to emergency physicians concerns the use of low-dose hydrocortisone only in cases of persistent hemodynamic instability (patient fails to respond to intravenous fluid and vasopressor therapy). The use of empiric corticosteroid administration is no longer recommended in all patients with shock. The rationale for this recommendation is that clinical trials and meta-analytic data have found mixed results about the effect of low-dose corticosteroids on mortality for the treatment of septic shock.29,30 However, the data do seem to suggest a favorable effect of steroid treatment on the endpoint of earlier shock reversal. Therefore, treatment with low-dose corticosteroids is reasonable in patients with hemodynamic instability despite adequate intravenous fluid and vasopressor therapy. When used, continuous infusion rather than repetitive bolus injections is recommended. Additionally, routine testing for ACTH stimulation is no longer recommended as a method of determining steroid deficiency.

SOURCE CONTROL

We recommend that a specific anatomic diagnosis of infection requiring consideration for emergency source control (eg, necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible and that intervention be undertaken for source control within the first 12 hours after the diagnosis is made, if feasible (grade 1C).

We suggest that, when infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (ungraded).

If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (ungraded).

Related to antibiotics is the critical issue of source control. Adequate attention to emergency anatomic sources of infection (such as necrotizing fasciitis and intra-abdominal sources) should be considered and evaluated so to expedite surgical care, if necessary. A specific recommendation for intervention within 12 hours, if feasible, is now added. New to the guidelines, the least physiologically taxing method of source control is recommended because of a propensity for hemodynamic instability and high surgical risk of these patients. Additionally, a specific recommendation about a delayed approach to treatment of peripancreatic necrosis has been added this iteration of the guidelines. Finally, removal of intravascular devices suspected to be a source of sepsis is still recommended, though the 2012 guidelines add the caveat that this may be delayed until other vascular access has been established.

MECHANICAL VENTILATION

We recommend that clinicians target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (grade 1A versus 12 mL/kg).

We recommend that plateau pressures be measured in patients with acute respiratory distress syndrome and that the initial upper-limit goal for plateau pressures in a passively inflated lung be less than or equal to 30 cm H₂O (grade 1B).

We recommend that positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectrauma) (grade 1B).
We suggest strategies based on higher rather than lower levels of PEEP for patients with sepsis-induced moderate to severe acute respiratory distress syndrome (grade 2C).

We suggest that noninvasive mask ventilation be used in that minority of sepsis-induced acute respiratory distress syndrome patients for whom the benefits of noninvasive mask ventilation have been carefully considered and are thought to outweigh the risks (grade 2B).

The guidelines continue to recommend a low-tidal-volume strategy (6 versus 12 mL/kg predicted body weight) in the setting of sepsis-induced acute respiratory distress syndrome, based on a clinical trial demonstrating an absolute 9% all-cause reduction in mortality in patients treated with the low- versus high-tidal-volume strategy. Although these data suggest 6 mL/kg tidal volumes are preferable to 12 mL/kg, other volumes may be acceptable in some patients when accounting for factors such as the plateau pressure, level of PEEP chosen, compliance of the thoracoabdominal compartment, the patient’s breathing effort, and degree of acidosis.

The guidelines recommend measuring plateau pressures, which are directly related to tidal volumes, and ensuring that they do not exceed 30 cm H2O. Measurement of plateau pressure is simple and can be performed at the bedside. PEEP is also recommended to prevent the collapse of alveoli at end expiration and prevent the associated atelectotrauma. A minimum PEEP setting of greater than 5 cm H2O is usually required to prevent alveolar collapse, but the titration of PEEP to higher levels for patients with moderate to severe sepsis-induced acute respiratory distress syndrome, through either bedside measurements of compliance or severity of oxygen deficit, is a new addition to this version of the guidelines.

Finally, the recommendations about the use of noninvasive mechanical ventilation have been generalized from specific recommendations about who is an appropriate candidate to a general statement about appropriate consideration of the risks and benefits of noninvasive strategies, with an added caveat that this should be pursued in a minority of patients.

**GLUCOSE CONTROL**

We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level less than 180 mg/dL rather than an upper blood glucose less than 110 mg/dL (grade 1A).

We recommend that blood glucose values be monitored every 1 to 2 hours until glucose values and insulin infusion rates are stable and then every 4 hours thereafter (grade 1C).

We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (ungraded).

Although blood glucose control is not a priority in the ED management of severe sepsis for patients with rapid admission to the ICU, it may be considered for patients with prolonged ED boarding times. One large randomized clinical trial of tight (<110 mg/dL) versus less intensive (<180 mg/dL) blood glucose management found no difference in patient-centered outcomes but a higher rate of adverse events in the tight glucose control group. According to these data, a blood glucose goal of less than 180 mg/dL is now recommended. Furthermore, a protocolized approach, ideally using arterial blood or serum rather than capillary blood, is recommended to minimize blood glucose variability, which has been associated with adverse outcomes.

**BICARBONATE THERAPY**

We recommend against the use of sodium bicarbonate therapy for improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH greater than or equal to 7.15 (grade 2B).

This recommendation remains unchanged from previous versions of the guidelines. In the setting of lactic acidosis, blinded clinical trial data fail to demonstrate superiority of bicarbonate therapy to saline solution in terms of hemodynamics, though the number of patients with a pH less than 7.15 was low and its effects in this group of patients are currently unknown.

### TO BE COMPLETED WITHIN 3 HOURS

- Measure lactate level
- Obtain blood cultures before administration of antibiotics
- Administer broad-spectrum antibiotics
- Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

### TO BE COMPLETED WITHIN 6 HOURS

- Apply vaspressors (for hypotension that does not respond to fluid resuscitation) to maintain a MAP ≥65 mm Hg
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L:
  - measure CVP*
  - measure central SvO2*
- Re-measure lactate if initial lactate level was elevated*
  *
  *Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, SvO2 of ≥70%, and normalization of lactate.

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**Figure 2.** Surviving Sepsis Campaign bundle. Adapted from: Surviving Sepsis Campaign 2012 Guidelines.
ACTIVATED PROTEIN C

Activated protein C has been voluntarily removed from the commercial market and is no longer available for use after the completion of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock trial, which failed to demonstrate any survival benefit in the subgroup of patients previously thought to benefit from activated protein C treatment. In light of this withdrawal, the Surviving Sepsis Campaign Guidelines provide a brief history about the evolution in the recommendations for use by the Surviving Sepsis Campaign.

SURVIVING SEPSIS CAMPAIGN CARE BUNDLE

The Surviving Sepsis Campaign provides a list of interventions to be completed within both 3 and 6 hours of triage (named the sepsis care bundle; delineated in Figure 2). The 2012 care bundle has changed since 2008. Again, in some circumstances there are internal inconsistencies between the actual guidelines and the care bundle goals, as discussed previously.

CONCLUSION

The 2012 Surviving Sepsis Campaign introduced several important changes in their recommendations for the treatment of severe sepsis and septic shock. The use of protocolized quantitative resuscitation with specific physiologic targets, preferential use of crystalloids (with or without albumin) for volume resuscitation, preferential use of norepinephrine, addition of lactate clearance as a marker of tissue hypoperfusion, a decreased emphasis on the use of corticosteroids, and removal of activated protein C are among the most relevant changes for emergency physicians to integrate into their practice.

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