Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008*

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Objective: **To provide an update to the original Surviving Sepsis Campaign clinical management guidelines, "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," published in 2004.**

Design: **Modified Delphi method with a consensus conference of 55 international experts, several subsequent meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. This process was conducted independently of any industry funding.**

Methods: **We used the Grades of Recommendation, 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. 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. In areas without complete agreement, a formal process of resolution was developed and applied. Recommendations are grouped into those directly targeting severe sepsis, recommendations targeting general care of the critically ill patient that are considered high priority in severe sepsis, and pediatric considerations.**

Results: **Key recommendations, listed by category, include early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures before antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 hr of diagnosis of septic shock (1B) and severe sepsis without septic shock (1D); reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate (1C); a usual 7–10 days of antibiotic therapy guided by clinical response (1D); source control with attention to the balance of risks and benefits of the chosen method (1C); administration of either crystalloid or colloid fluid resuscitation (1B); fluid challenge to restore mean circulating filling pressure (1C); reduction in rate of fluid administration with rising filing pressures and no improvement in tissue perfusion (1D); vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure ≥65 mm Hg (1C); dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy (1C); stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for postoperative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7–9 g/dL (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/analgesia (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuromuscular blockers, if at all possible (1B); institution of glycemic control (1B), targeting a blood glucose <150 mg/dL after initial stabilization (2C); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1A); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding using H2 blockers (1A) or proton pump inhibitors (1B); and consideration of limitation of support where appropriate (1D). Recommendations specific to pediatric severe sepsis include greater use of physical examination therapeutic end points (2C); dopamine as the first drug of choice for hypotension (2C); steroids only in children with suspected or proven adrenal insufficiency (2C); and a recommendation against the use of recombinant activated protein C in children (1B).**

Conclusions: **There was strong agreement among a large cohort of international experts regarding many level 1 recommendations for the best current care of patients with severe sepsis. Evidenced-based recommendations regarding the acute management of sepsis and septic shock are the first step toward improved outcomes for this important group of critically ill patients.**

Key Words: sepsis; severe sepsis; septic shock; sepsis syndrome; infection; Grades of Recommendation, Assessment, Development and Evaluation criteria; GRADE; guidelines; evidence-based medicine; Surviving Sepsis Campaign; sepsis bundles

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Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major healthcare problems, affecting millions of individuals around the world each year, killing one in four (and often more), and increasing in incidence (1–5). Similar to polytrauma, acute myocardial infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcome. In 2004, an international group of experts in the diagnosis and management of infection and sepsis, representing 11 organizations, published the first internationally accepted guidelines that the bedside clinician could use to improve outcomes in severe sepsis and septic shock (6, 7). These guidelines represented phase II of the Surviving Sepsis Campaign (SSC), an international effort to increase awareness and improve outcomes in severe sepsis. Joined by additional organizations, the group met again in 2006 and 2007 to update the guidelines document using a new evidence-based methodology system for assessing quality of evidence and strength of recommendations (8–11).

These recommendations are intended to provide guidance for the clinician caring for a patient with severe sepsis or septic shock. Recommendations from these guidelines cannot replace the clinician's decision-making capability when he or she is provided with a patient's unique set of clinical variables. Most of these recommendations are appropriate for the severe sepsis patient in both the intensive care unit (ICU) and non-ICU settings. In fact, the committee believes that currently, the greatest outcome improvement can be made through education and process change for those caring for severe sepsis patients in the non-ICU setting and across the spectrum of acute care. It should also be noted that resource limitations in some institutions and countries may prevent physicians from accomplishing particular recommendations.

Scheme 1. Diagnostic criteria for sepsis

- Infection, documented or suspected, and some of the following:
  - General variables
    - Fever (>38.3°C)
    - Hypothermia (core temperature <36°C)
    - Heart rate >90 min^{-1} or >2 SD above the normal value for age
    - Tachypnea
    - Altered mental status
    - Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
    - Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
  - Inflammatory variables
    - Leukocytosis (WBC count >12,000 μL^{-1})
    - Leukopenia (WBC count <4000 μL^{-1})
    - Normal WBC count with >10% immature forms
    - Plasma C-reactive protein >2 SD above the normal value
    - Plasma procalcitonin >2 SD above the normal value
  - Hemodynamic variables
    - Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
- Organ dysfunction variables
  - Arterial hypoxemia (Pao_2/Fio^2 <300)
  - Acute oliguria (urine output <0.5 mL/Kg hr or 45 mmol/L for at least 2 hrs, despite adequate fluid resuscitation)
  - Creatinine increase >0.5 mg/dL or 44.2 μmol/L
  - Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count, <100,000 μL^{-1})
  - Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)
- Tissue perfusion variables
  - Hyperlactatemia (> upper limit of lab normal)
  - Decreased capillary refill or mottling
- Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; INR, international normalized ratio; a PTT, activated partial thromboplastin time.

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256

Scheme 2.

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

ALI, acute lung injury; INR, international normalized ratio.

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256. ACCP/SCCM Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874

METHODS

Sepsis is defined as infection plus systemic manifestations of infection (Scheme 1) (12). Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. The threshold for this dysfunction has varied somewhat from one severe sepsis research study to another. An example of typical thresholds identification of severe sepsis is shown in Scheme 2 (12, 13). Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure <70 mm Hg or a SBP decrease >40 mm Hg or <2 SD below normal for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting de-

spite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as either septic shock, an elevated lactate, or oliguria.

The current clinical practice guidelines build on the first and second editions from 2001 (discussed subsequently) and 2004 (6, 7, 14). The 2001 publication incorporated a MEDLINE search for clinical trials in the preceding 10 yrs, supplemented by a manual search of other relevant journals (14). The 2004 publication incorporated the evidence available through the end of 2003. The current publication is based on an updated search into 2007 (see following methods and rules).

The 2001 guidelines were coordinated by the International Sepsis Forum; the 2004 guidelines were funded by unrestricted educational grants from industry and administered through the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. Two of the SSC administering organizations receive unrestricted industry funding to support SSC activities (ESICM and SCCM), but none of this funding was used to support the 2006/2007 committee meetings.

It is important to distinguish between the process of guidelines revision and the SSC. The SSC is partially funded by unrestricted educational industry grants, including those from Edwards Life-Sciences, Eli Lilly and Company, and Philips Medical Systems. SSC also received funding from the Coalition for Critical Care Excellence of the Society of Critical Care Medicine. The great majority of industry funding has come from Eli Lilly and Company.

Current industry funding for the SSC is directed to the performance improvement initiative. No industry funding was used in the guidelines revision process.

For both the 2004 and the 2006/2007 efforts, there were no members of the committee from industry, no industry input into guidelines development, and no industry presence at any of the meetings. Industry awareness or comment on the recommendations was not allowed. No member of the guideline committee received any honoraria for any role in the 2004 or 2006/2007 guidelines process. The committee considered the issue of recusement of individual committee members during deliberation and decision making in areas where committee members had either financial or academic competing interests; however, consensus as to threshold for exclusion could not be reached. Alternatively, the committee agreed to ensure full disclosure and transparency of all committee members' potential conflicts at time of publication. (See disclosures at the end of this document.)

The guidelines process included a modified Delphi method, a consensus conference, several subsequent meetings of subgroups and key individuals, teleconferences and electronic-based discussions among subgroups and members of the entire committee, and two follow-up nominal group meetings in 2007.

Subgroups were formed, each charged with updating recommendations in specific areas, including corticosteroids, blood products, activated protein C, renal replacement therapy, antibiotics, source control, and glucose control. Each subgroup was responsible for updating the evidence (into 2007, with major additional elements of information incorporated into the evolving manuscript throughout 2006 and 2007). A separate search was performed for each clearly defined question. The committee chair worked with subgroup heads to identify pertinent search terms that always included, at a minimum, sepsis, severe sepsis, septic shock, and sepsis syndrome crossed against the general topic area of the subgroup as well as pertinent key words of the specific question posed. All questions of the previous guidelines publications were searched, as were pertinent new questions generated by general topic-related search or recent trials. Quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (discussed subsequently). Significant education of committee members on the GRADE approach was performed via e-mail before the first committee meeting and at the first meeting. Rules were distributed concerning assessing the body of evidence, and GRADE experts were available for questions throughout the process. Subgroups agreed electronically on draft proposals that were presented to committee meetings for general discussion. In January 2006, the entire group met during the 35th SCCM Critical Care Congress in San Francisco, California. The results of that discussion were incorporated into the next version of recommendations and again discussed using electronic mail. Recommendations were finalized during nominal group meetings (composed of a subset of the committee members) at the 2007 SCCM (Orlando, FL) and 2007 International Symposium on Intensive Care and Emergency Medicine (Brussels) meetings with recirculation of deliberations and decisions to the entire group for comment or approval. At the discretion of the chair and following adequate discussion, competing proposals for wording of recommendations or assigning strength of evidence were resolved by formal voting. On occasions, voting was performed to give the committee a sense of distribution of opinions to facilitate additional discussion. The manuscript was edited for style and form by the writing committee with final approval by section leads for their respective group assignment and then by the entire committee.

The development of guidelines and grading of recommendations for the 2004 guideline development process were based on a system proposed by Sackett (15) in 1989, during one of the first American College of Chest Physicians (ACCP) conferences on the use of antithrombotic therapies. The revised guidelines recommendations are based on the GRADE system, a structured system for rating quality of evidence and grading strength of recommendation in clinical practice (8–11). The SSC Steering Committee and individual authors collaborated with GRADE representatives to apply the GRADE system to the SSC guidelines revision process. The members of GRADE group were directly involved, either in person or via e-mail, in all discussions and deliberations among the guidelines committee members as to grading decisions. Subsequently, the SSC authors used written material prepared by the GRADE group and conferred with GRADE group members who were available at the first committee meeting and subsequent nominal group meetings. GRADE representatives were also used as a resource throughout subgroup deliberation.

The GRADE system is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between benefits vs. risks, burden, and cost and, based on the preceding, development and grading of a management recommendations (9–11). Keeping the rating of quality of evidence and strength of recommendation explicitly separate constitutes a crucial and defining feature of the GRADE approach. This system classifies quality of evidence as high (grade A), mod-

erate (grade B), low (grade C), or very low (grade D). Randomized trials begin as high-quality evidence but may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias (Table 1). Examples of indirectness of the evidence include population studied, interventions used, outcomes measured, and how these relate to the question of interest. Observational (nonrandomized) studies begin as low-quality evidence, but the quality level may be upgraded on the basis of large magnitude of effect. An example of this is the quality of evidence for early administration of antibiotics.

The GRADE system classifies recommendations as strong (grade 1) or weak (grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. The committee assessed whether the desirable effects of adherence will outweigh the undesirable effects, and the strength of a recommendation reflects the group's degree of confidence in that assessment (Table 2). A strong recommendation in favor of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients, and cost savings) will clearly outweigh the undesirable effects (harms, more burden, and greater costs). A weak recommendation in favor of an intervention indicates that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these tradeoffs—either because some of the evidence is low quality (and thus there remains uncertainty regarding the benefits and risks) or the benefits and downsides are closely balanced. While the degree of confidence is a continuum and there is no precise threshold between a strong and a weak recommendation, the presence of important concerns about one or more of the preceding factors makes a weak recommendation more likely. A strong recommendation is worded as "we recommend" and a weak recommendation as "we suggest."

The implications of calling a recommendation strong are that most well-informed patients would accept that intervention and that most clinicians should use it in most situations. There may be circumstances in which a strong recommendation cannot or should not be followed for an individual patient because of that patient's preferences or clinical characteristics that make the recommendation less applicable. Being a strong recommendation does not automatically imply standard of care. For example, the strong recommendation for administering antibiotics within 1 hr of the diagnosis of severe sepsis, although desirable, is not currently standard of care as verified by current practice (M Levy, personal communication, from first 8,000 patients entered internationally into the SSC performance improvement database). The implication of a weak recommendation is that although a majority of well-informed patients would accept it (but a substantial proportion would not), clinicians should consider its use according to particular circumstance.

Differences of opinion among committee members about interpretation of evidence, wording of proposals, or strength of recommendations were resolved using a specifically developed set of rules. We will describe this process in detail in a separate publication. In summary, the main approach for converting diverse opinions into a recommendation was as follows: 1) to give a recommendation a direction (for or against the given action), a majority of votes were to be in favor of that direction, with ≤20% preferring the opposite direction (there was a neutral vote allowed as well); 2) to call a given recommendation strong rather than weak, ≥70% "strong" votes were required; 3) if <70% of votes indicated "strong" preference, the recommendation was assigned a weak category of strength. We used a combination of modified Delphi process and nominal (expert) group techniques to ensure both depth and breadth of review. The entire review group (together with their parent organizations as required) participated in the larger, iterative, modified Delphi process. The smaller working group meetings, which took place in person, functioned as the nominal groups. If a clear consensus could not be obtained by polling within the nominal group meetings, the larger group was specifically asked to use the polling process. This was only required for corticosteroids

Table 1. Determination of the quality of evidence

- 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
- Main factors that may increase the strength of evidence
  1. Large magnitude of effect (direct evidence, 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

RCT, randomized controlled trial; RR, relative risk.

Table 2. Factors determining strong vs. weak recommendation

What Should Be Considered	Recommended Process
Quality of evidence	The lower the quality of evidence, the less likely a strong recommendation
Relative importance of the outcomes	If values and preferences vary widely, a strong recommendation becomes less likely
Baseline risks of outcomes	The higher the risk, the greater the magnitude of benefit
Magnitude of relative risk, including benefits, harms, and burden	Larger relative risk reductions or larger increases in relative risk of harm make a strong recommendation more or less likely, respectively
Absolute magnitude of the effect	The larger the absolute benefits and harms, the greater or lesser likelihood, respectively, of a strong recommendation
Precision of the estimates of the effects	The greater the precision, the more likely a strong recommendation
Costs	The higher the cost of treatment, the less likely a strong recommendation

and glycemic control. The larger group had the opportunity to review all outputs. In this way the entire review combined intense focused discussion (nominal group) with broader review and monitoring using the Delphi process.

Note: Refer to Tables 3–5 for condensed adult recommendations.

I. MANAGEMENT OF SEVERE SEPSIS

A. Initial Resuscitation

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

   Central venous pressure 8–12 mm Hg

   Mean arterial pressure (MAP) ≥65 mm Hg

   Urine output ≥0.5 mL·kg^{-1}·hr $^{-1}$

   Central venous (superior vena cava) or mixed venous oxygen saturation ≥70% or ≥65%, respectively (grade 1C)

Rationale. Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study (16). Resuscitation directed toward the previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known preexisting decreased ventricular compliance, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the impediment to filling (17). Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction (18). Elevated central venous pressures may also be seen with preexisting clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Recently published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥65 mm Hg as well as central venous oxygen saturation ($Scvo_2$, measured in superior vena cava, either intermittently or continuously) of ≥70% (19). Many recent studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion (20–25). Studies of patients with shock indicate that mixed venous oxygen saturation ($S\bar{V}o_2$) runs 5–7% lower than central venous oxygen saturation ($Scvo_2$) (26) and that an early goal-directed resuscitation protocol can be established in a nonresearch general practice venue (27).

Table 3. Initial resuscitation and infection issues

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

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

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

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

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

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; ICU, intensive care unit; CVP, central venous pressure; BC, blood culture.

[a]A higher target CVP of 12–15 mm Hg is recommended in the presence of mechanical ventilation or preexisting decreased ventricular compliance.

Table 4. Hemodynamic support and adjunctive therapy

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

Fluid therapy
- ● Fluid-resuscitate using crystalloids or colloids (1B)
- ● Target a CVP of ≥8 mm Hg (≥12 mm Hg if mechanically ventilated) (1C)
- ● Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- ● Give fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. 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)

Vasopressors
- ● Maintain MAP ≥65 mm Hg (1C)
- ● Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- ○ Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- ○ Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- ● Do not use low-dose dopamine for renal protection (1A)
- ● In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

Inotropic therapy
- ● Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- ● Do not increase cardiac index to predetermined supranormal levels (1B)

Steroids
- ○ 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 μg 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 sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D)

Recombinant human activated protein C
- ○ 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 (2B, 2C for postoperative patients).
- ● Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC (1A)

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; CVP, central venous pressure; MAP, mean arterial pressure; ACTH, adrenocorticotropic hormone; rhAPC, recombinant human activated protein C; APACHE, Acute Physiology and Chronic Health Evaluation.

There are recognized limitations to ventricular filling pressure estimates as surrogates for fluid resuscitation (28, 29). However, measurement of central venous pressure is currently the most readily obtainable target for fluid resuscitation. There may be advantages to targeting fluid resuscitation to flow and perhaps to volumetric indices (and even to microcirculation changes) (30–33). Technologies currently exist that allow measurement of flow at the bedside (34, 35). Future goals should be making these technologies more accessible during the critical early resuscitation period and research to validate utility. These technologies are already available for early ICU resuscitation.

2. We suggest that during the first 6 hrs of resuscitation of severe sepsis or septic shock, if $Scvo_2$ or $S\bar{V}o_2$ of 70% or 65%, respectively, is not achieved with fluid resuscitation to the central venous pressure target, then transfusion of packed red blood cells to achieve a hematocrit of ≥30% and/or administration of a dobutamine infusion (up to a maximum of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) be used to achieve this goal (grade 2C).

Rationale. The protocol used in the study cited previously targeted an increase in $Scvo_2$ to ≥70% (16). This was achieved by sequential institution of initial fluid resuscitation, packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if hematocrit is <30%) or dobutamine the best initial choice to increase oxygen delivery and thereby elevate $Scvo_2$, when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing oxygen content or increasing cardiac output) of the protocol on achievement of improved outcome.

B. Diagnosis

1. We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay in antibiotic administration. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antibiotics with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hrs) inserted. Cultures of other sites (preferably quantitative where 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 antibiotic therapy if not associated with significant delay in antibiotic administration (grade 1C).

Rationale. Although sampling should not delay timely administration of antibiotics in patients with severe sepsis (e.g., lumbar puncture in suspected meningitis), obtaining appropriate cultures before administration of antibiotics is essential to confirm infection and the responsible pathogens and to allow de-escalation of antibiotic therapy after receipt of the susceptibility profile. Samples can be refrigerated or frozen if processing cannot be performed immediately. Immediate transport to a microbiological lab is necessary. Because rapid sterilization of blood cultures can occur within a few hours after the first antibiotic dose, obtaining those cultures before starting therapy is essential if the causative organ-

Table 5. Other supportive therapy of severe sepsis

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

Blood product administration
- ● Give red blood cells when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin of 7.0–9.0 g/dL in adults (1B). A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischaemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis)
- ● Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons (1B)
- ○ Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (2D)
- ● Do not use antithrombin therapy (1B)
- ○ Administer platelets when (2D)
  Counts are $<5000/mm^3$ (5×10^9/L) regardless of bleeding
  Counts are $5000–30{,}000/mm^3$ ($5–30 \times 10^9$/L) and there is significant bleeding risk
  Higher platelet counts ($\geq 50{,}000/mm^3$ [50×10^9/L]) are required for surgery or invasive procedures

Mechanical ventilation of sepsis-induced ALI/ARDS
- ● Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B)
- ● Target an initial upper limit plateau pressure ≤30 cm H_2O. Consider chest wall compliance when assessing plateau pressure (1C)
- ● Allow $Paco_2$ 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)
- ○ Consider using the prone position for ARDS patients requiring potentially injurious levels of Fio_2 or plateau pressure, provided they are not put at risk from positional changes (2C)
- ● Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated (1B), between 30° and 45° (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)
- ● Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation (1A)
  - ● SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H_2O 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
    require Fio_2 levels that can be safely delivered with a face mask or nasal cannula
- ● Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (1A)
- ● Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion (1C)

Sedation, analgesia, and neuromuscular blockade in sepsis
- ● Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients (1B)
- ● Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-titrate if necessary (1B)
- ● Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions (1B)

Glucose control
- ● Use intravenous 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)

Renal replacement
- ○ Intermittent hemodialysis and CVVH are considered equivalent (2B)
- ○ CVVH offers easier management in hemodynamically unstable patients (2D)

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)

Deep vein thrombosis prophylaxis
- ● Use either low-dose UFH or LMWH, unless contraindicated (1A)
- ● Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A)
- ○ Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C)
- ○ In patients at very high risk, LMWH should be used rather than UFH (2C)

Stress ulcer prophylaxis
- ● Provide stress ulcer prophylaxis using H2 blocker (1A) or proton pump inhibitor (1B). Benefits of prevention of upper gastrointestinal 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 (1D)

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; SBT, spontaneous breathing trial; ICU, intensive care unit; CVVH, continuous veno-venous hemofiltration; UFH, unfractionated heparin; LMWH, low-molecular weight heparin.

ism is to be identified. Two or more blood cultures are recommended (36). In patients with indwelling catheters (for >48 hrs), at least one blood culture should be drawn through each lumen of each vascular access device. Obtaining blood cultures peripherally and through a vascular access device is an important strategy. If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e., >2 hrs

earlier), the data support the concept that the vascular access device is the source of the infection (37). Quantitative cultures of catheter and peripheral blood are also useful for determining whether the catheter is the source of infection. Volume of blood drawn with the culture tube should be ≥10 mL (38). Quantitative (or semiquantitative) cultures of respiratory tract secretions are recommended for the diagnosis of ventilator-associated pneumonia (39). Gram-negative stain can be useful, in particular for respiratory tract specimens, to help decide the microorganisms to be targeted. The potential role of biomarkers for diagnosis of infection in patients presenting with severe sepsis remains undefined. The procalcitonin level, although often useful, is problematic in patients with an acute inflammatory pattern from other causes (e.g., postoperative, shock) (40). In the near future, rapid diagnostic methods (polymerase chain reaction, micro-arrays) might prove extremely helpful for a quicker identification of pathogens and major antimicrobial resistance determinants (41).

2. We recommend that imaging studies be performed promptly in attempts to confirm a potential source of infection. Sampling of potential sources of infection should occur as they are identified; however, some patients may be too unstable to warrant certain invasive procedures or transport outside of the ICU. Bedside studies, such as ultrasound, are useful in these circumstances (grade 1C).

Rationale. Diagnostic studies may identify a source of infection that requires removal of a foreign body or drainage to maximize the likelihood of a satisfactory response to therapy. However, even in the most organized and well-staffed healthcare facilities, transport of patients can be dangerous, as can placing patients in outside-unit imaging devices that are difficult to access and monitor. Balancing risk and benefit is therefore mandatory in those settings.

C. Antibiotic Therapy

1. We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1D). Appropriate cultures should be obtained before initiating antibiotic therapy but should not prevent prompt administration of antimicrobial therapy (grade 1D).

Rationale. Establishing vascular access and initiating aggressive fluid resuscitation are the first priority when managing patients with severe sepsis or septic shock. However, prompt infusion of antimicrobial agents should also be a priority and may require additional vascular access ports (42, 43). In the presence of septic shock, each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality (42). If antimicrobial agents cannot be mixed and delivered promptly from the pharmacy, establishing a supply of premixed antibiotics for such urgent situations is an appropriate strategy for ensuring prompt administration. In choosing the antimicrobial regimen, clinicians should be aware that some antimicrobial agents have the advantage of bolus administration, while others require a lengthy infusion. Thus, if vascular access is limited and many different agents must be infused, bolus drugs may offer an advantage.

2a. We recommend that initial empirical anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal) and that penetrate in adequate concentrations into the presumed source of sepsis (grade 1B).

Rationale. The choice of empirical antibiotics depends on complex issues related to the patient's history, including drug intolerances, underlying disease, the clinical syndrome, and susceptibility patterns of pathogens in the community, in the hospital, and that previously have been documented to colonize or infect the patient. There is an especially wide range of potential pathogens for neutropenic patients.

Recently used antibiotics should generally be avoided. When choosing empirical therapy, clinicians should be cognizant of the virulence and growing prevalence of oxacillin (methicillin)-resistant *Staphylococcus aureus* (ORSA or MRSA) in some communities and healthcare settings (especially in the United States). If the prevalence is significant, and in consideration of the virulence of this organism, empirical therapy adequate for this pathogen would be warranted. Clinicians should also consider whether candidemia is a likely pathogen when choosing initial therapy. When deemed warranted, the selection of empirical antifungal therapy (e.g., fluconazole, amphotericin B, or echinocandin) will be tailored to the local pattern of the most prevalent *Candida* species and any prior administration of azoles drugs (44). Risk factors for candidemia should also be considered when choosing initial therapy.

Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens. There is ample evidence that failure to initiate appropriate therapy (i.e., therapy with activity against the pathogen that is subsequently identified as the causative agent) correlates with increased morbidity and mortality (45–48).

Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antibiotic susceptibilities are defined. Restriction of antibiotics as a strategy to reduce the development of antimicrobial resistance or to reduce cost is not an appropriate initial strategy in this patient population.

All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. Drug serum concentration monitoring can be useful in an ICU setting for those drugs that can be measured promptly. An experienced physician or clinical pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity (49–52).

2b. We recommend that the antimicrobial regimen be reassessed daily to optimize activity, to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1C).

Rationale. Although restriction of antibiotics as a strategy to reduce the development of antimicrobial resistance or to reduce cost is not an appropriate initial strategy in this patient population, once the causative pathogen has been identified, it may become apparent that none of the empirical drugs offers optimal therapy; that is, there may be another drug proven to produce superior clinical out-

come that should therefore replace empirical agents.

Narrowing the spectrum of antibiotic coverage and reducing the duration of antibiotic therapy will reduce the likelihood that the patient will develop superinfection with pathogenic or resistant organisms, such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*. However, the desire to minimize superinfections and other complications should not take precedence over the need to give the patient an adequate course of therapy to cure the infection that caused the severe sepsis or septic shock.

2c. We suggest combination therapy for patients with known or suspected *Pseudomonas* infections as a cause of severe sepsis (grade 2D).

2d. We suggest combination empirical therapy for neutropenic patients with severe sepsis (grade 2D).

2e. When used empirically in patients with severe sepsis, we suggest that combination therapy should not be administered for >3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2D).

Rationale. Although no study or meta-analysis has convincingly demonstrated that combination therapy produces a superior clinical outcome for individual pathogens in a particular patient group, combination therapies do produce *in vitro* synergy against pathogens in some models (although such synergy is difficult to define and predict). In some clinical scenarios, such as the two preceding, combination therapies are biologically plausible and are likely clinically useful even if evidence has not demonstrated improved clinical outcome (53–56). Combination therapy for suspected known *Pseudomonas* pending sensitivities increases the likelihood that at least one drug is effective against that strain and positively affects outcome (57).

3. We recommend that the duration of therapy typically be 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, or immunologic deficiencies, including neutropenia (grade 1D).

4. We recommend that if the presenting clinical syndrome is determined to be due to a noninfectious cause, antimicrobial therapy be stopped promptly to minimize the likelihood that the patient will become infected with an antibiotic-resistant pathogen or will develop a drug-related adverse effect (grade 1D).

Rationale. Clinicians should be cognizant that blood cultures will be negative in >50% of cases of severe sepsis or septic shock, yet many of these cases are very likely caused by bacteria or fungi. Thus, the decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.

D. Source Control

1a. We recommend that a specific anatomical diagnosis of infection requiring consideration for emergent source control (e.g., necrotizing fasciitis, diffuse peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible (grade 1C) and within the first 6 hrs following presentation (grade 1D).

1b. We further recommend that all patients presenting with severe sepsis be evaluated for the presence of a focus on infection amenable to source control measures, specifically the drainage of an abscess or local focus on infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination (grade 1C). (Appendix A provides examples of potential sites needing source control.)

2. 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).

3. We recommend that when source control is required, the effective intervention associated with the least physiologic insult be employed (e.g., percutaneous rather than surgical drainage of an abscess (grade 1D).

4. We recommend that when intravascular access devices are a possible source of severe sepsis or septic shock, they be promptly removed after other vascular access has been established (grade 1C).

Rationale. The principals of source control in the management of sepsis include a rapid diagnosis of the specific site of infection and identification of a focus on infection amenable to source control measures (specifically the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) (58). Foci of infection readily amenable to source control measures include an intra-abdominal abscess or gastrointestinal perforation, cholangitis or pyelonephritis, intestinal ischemia or necrotizing soft tissue infection, and other deep space infection, such as an empyema or septic arthritis. Such infectious foci should be controlled as soon as possible following successful initial resuscitation (59), accomplishing the source control objective with the least physiologic upset possible (e.g., percutaneous rather than surgical drainage of an abscess [60], endoscopic rather than surgical drainage of biliary tree), and removing intravascular access devices that are potentially the source of severe sepsis or septic shock promptly after establishing other vascular access (61, 62). A randomized, controlled trial comparing early vs. delayed surgical intervention for peripancreatic necrosis showed better outcomes with a delayed approach (63). However, areas of uncertainty exist, such as definitive documentation of infection and appropriate length of delay. The selection of optimal source control methods must weigh benefits and risks of the specific intervention as well as risks of transfer (64). Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. Surgical intervention should be considered when lesser interventional approaches are inadequate or when diagnostic uncertainty persists despite radiologic evaluation. Specific clinical situations require consideration of available choices, patient's preferences, and clinician's expertise.

E. Fluid Therapy

1. We recommend fluid resuscitation with either natural/artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another (grade 1B).

Rationale. The SAFE study indicated that albumin administration was safe and equally as effective as crystalloid (65). There was an insignificant decrease in mortality rates with the use of colloid in a subset

analysis of septic patients ($p = .09$). Previous meta-analyses of small studies of ICU patients had demonstrated no difference between crystalloid and colloid fluid resuscitation (66–68). Although administration of hydroxyethyl starch may increase the risk of acute renal failure in patients with sepsis, variable findings preclude definitive recommendations (69, 70). As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. Crystalloids are less expensive.

2. We recommend that fluid resuscitation initially target a central venous pressure of ≥8 mm Hg (12 mm Hg in mechanically ventilated patients). Further fluid therapy is often required (grade 1C).

3a. We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as the hemodynamic improvement (e.g., arterial pressure, heart rate, urine output) continues (grade 1D).

3b. We recommend that fluid challenge in patients with suspected hypovolemia be started with ≥1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. More rapid administration and greater amounts of fluid may be needed in patients with sepsis-induced tissue hypoperfusion (see Initial Resuscitation recommendations) (grade 1D).

3c. We recommend that the rate of fluid administration be reduced substantially when cardiac filling pressures (central venous pressure or pulmonary artery balloon-occluded pressure) increase without concurrent hemodynamic improvement (grade 1D).

Rationale. Fluid challenge must be clearly separated from simple fluid administration; it is a technique in which large amounts of fluids are administered over a limited period of time under close monitoring to evaluate the patient's response and avoid the development of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hrs of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period.

F. Vasopressors

1. We recommend that mean arterial pressure (MAP) be maintained ≥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 certain mean arterial pressure, autoregulation in various 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 (71, 72). The titration of norepinephrine to as low as MAP 65 mm Hg has been shown to preserve tissue perfusion (72). In addition, preexisting comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive, a lower MAP might be adequate. Supplementing end points, such as blood pressure, with assessment of regional and global perfusion, such as blood lactate concentrations 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, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs, great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

2. We recommend either norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available) (grade 1C).

3a. We suggest that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (grade 2C). Vasopressin 0.03 units/min may be added to norepinephrine subsequently with anticipation of an effect equivalent to that of norepinephrine alone.

3b. We suggest that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine (grade 2B).

Rationale. There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock (73–85). Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. 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 (86). It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (87). Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits (88–93). Terlipressin has similar effects but is long lasting (94). Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock the concentration decreases to normal range in the majority of patients between 24 and 48 hrs (95). This has been called *relative vasopressin deficiency* because in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vaso-

pressin at 0.03 units/min, showed no difference in outcome in the intent to treat population. An *a priori* defined subgroup analysis showed that the survival of patients receiving <15 μg/min norepinephrine at the time of randomization was better with vasopressin. However, the pretrial rationale for this stratification was based on exploring potential benefit in the ≥15 μg norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed (96). Cardiac output measurement to allow maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.

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

Rationale. A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in either primary outcomes (peak serum creatinine, need for renal replacement, urine output, time to recovery of normal renal function) or secondary outcomes (survival to either ICU or hospital discharge, ICU stay, hospital stay, arrhythmias) (97, 98). Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function.

6. We recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (grade 1D).

Rationale. In shock states, estimation of blood pressure using a cuff is commonly inaccurate; use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure. These catheters also allow continuous analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.

G. Inotropic Therapy

1. We recommend that a dobutamine infusion be administered in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output (grade 1C).
2. We recommend against the use of a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

Rationale. Dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure. Septic patients who remain hypotensive after fluid resuscitation may have low, normal, or increased cardiac outputs. Therefore, treatment with a combined inotrope/vasopressor, such as norepinephrine or dopamine, is recommended if cardiac output is not measured. When the capability exists for monitoring cardiac output in addition to blood pressure, a vasopressor, such as norepinephrine, may be used separately to target specific levels of mean arterial pressure and cardiac output. Two large prospective clinical trials that included critically ill ICU patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal targets by use of dobutamine (99, 100). These studies did not specifically target patients with severe sepsis and did not target the first 6 hrs of resuscitation. The first 6 hrs of resuscitation of sepsis-induced hypoperfusion need to be treated separately from the later stages of severe sepsis (see Initial Resuscitation recommendations).

H. Corticosteroids

1. We suggest that intravenous hydrocortisone be given *only* to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).

Rationale. One French multicenter, randomized controlled trial (RCT) of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors) showed a significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as postadrenocorticotropic hormone [ACTH] cortisol increase ≤9 μg/dL) (101). Two additional smaller RCTs also showed significant effects on shock reversal with steroid therapy (102, 103). However, a recent large, European multicenter trial (CORTICUS), which has been presented in abstract form but not yet published, failed to show a mortality benefit with steroid therapy of septic shock (104). CORTICUS did show a faster resolution of septic shock in patients who received steroids. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. Importantly, unlike the French trial, which only enrolled shock patients with blood pressure unresponsive to vasopressor therapy, the CORTICUS study included patients with septic shock, regardless of how the blood pressure responded to vasopressors. Although corticosteroids do appear to promote shock reversal, the lack of a clear improvement in mortality—coupled with known side effects of steroids, such as increased risk of infection and myopathy—generally tempered enthusiasm for their broad use. Thus, there was broad agreement that the recommendation should be downgraded from the previous guidelines (Appendix B). There was considerable discussion and consideration by the committee on the option of encouraging use in those patients whose blood pressure was unresponsive to fluids and vasopressors, while strongly discouraging use in subjects whose shock responded well to fluids and pressors. However, this more complex set of recommendations was rejected in favor of the preceding single recommendation (Appendix B).

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

Rationale. Although one study suggested those who did not respond to ACTH with a brisk surge in cortisol (failure to achieve or >9 μg/dL increase in cortisol 30–60 mins after ACTH administration) were more likely to benefit from steroids than those who did respond, the overall trial population appeared to benefit regardless of ACTH result, and the observation of a potential interaction between steroid use and ACTH test was not statistically significant (101). Furthermore, there was no evidence of this distinction between responders and nonresponders in a recent multicenter trial (104). Commonly used cortisol immunoassays measure total cortisol (protein-bound and free) while free cortisol is the pertinent measurement. The relationship between free and total cortisol varies with serum protein concentration. When compared with a reference method (mass spectrometry), cortisol immunoassays may over- or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders (105).

Although the clinical significance is not clear, it is now recognized that etomidate, when used for induction for intubation, will suppress the hypothalamic-pituitary-adrenal axis (106).

3. We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available (grade 2B).

Rationale. Although often proposed for use until an ACTH stimulation test can be administered, we no longer suggest an ACTH test in this clinical situation (see the preceding point 3). Furthermore, dexamethasone can lead to immediate and prolonged suppression of the hypothalamic-pituitary-adrenal axis after administration (107).

4. We suggest the daily addition of oral fludrocortisone (50 μg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (grade 2C).

Rationale. One study added 50 μg of fludrocortisone orally (101). Since hydrocortisone has intrinsic mineralocorticoid activity, there is controversy as to whether fludrocortisone should be added.

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

Rationale. There has been no comparative study between a fixed-duration and clinically guided regimen or between tapering and abrupt cessation of steroids. Three RCTs used a fixed-duration protocol for treatment (101, 103, 104), and in two RCTs, therapy was decreased after shock resolution (102, 108). In four RCTs steroids were tapered over several days (102–104, 108), and in two RCTs (101, 109) steroids were withdrawn abruptly. One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids (110). It remains uncertain whether outcome is affected by tapering of steroids.

6. We recommend that doses of corticosteroids comparable to >300 mg of hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (grade 1A).

Rationale. Two randomized prospective clinical trials and a meta-analyses concluded that for therapy of severe sepsis or septic shock, high-dose corticosteroid therapy is ineffective or harmful (111–113). Reasons to maintain higher doses of corticosteroid for medical conditions other than septic shock may exist.

7. We recommend that corticosteroids not be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress-dose steroids if the patient's endocrine or corticosteroid administration history warrants (grade 1D).

Rationale. No studies exist that specifically target severe sepsis in the absence of shock and offer support for use of stress doses of steroids in this patient population. Steroids may be indicated in the presence of a history of steroid therapy or adrenal dysfunction. A recent preliminary study of stress-dose level steroids in community-acquired pneumonia is encouraging but needs confirmation (114).

I. Recombinant Human Activated Protein C (rhAPC)

1. 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 Acute Physiology and Chronic Health Evaluation (APACHE) II ≥25 or multiple organ failure, receive rhAPC if there are no contraindications (grade 2B except for patients within 30 days of surgery, for whom it is grade 2C). Relative contraindications should also be considered in decision making.
2. 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).

Rationale. The evidence concerning use of rhAPC in adults is primarily based on two RCTs: PROWESS (1,690 adult patients, stopped early for efficacy) (115) and ADDRESS (stopped early for futility) (116). Additional safety information comes from an open-label observational study, ENHANCE (117). The ENHANCE trial also suggested that early administration of rhAPC was associated with better outcomes.

PROWESS involved 1,690 patients and documented 6.1% in absolute total mortality reduction with a relative risk reduction of 19.4%, 95% confidence interval 6.6–30.5%, and number needed to treat 16 (115). Controversy associated with the results focused on a number of subgroup analyses. Subgroup analyses have the potential to mislead due to the absence of an intent to treat, sampling bias, and selection error (118). The analyses suggested increasing absolute and relative risk reduction with greater risk of death using both higher APACHE II scores and greater number of organ failures (119). This led to drug approval for patients with high risk of death (such as APACHE II ≥25) and more than one organ failure in Europe.

The ADDRESS trial involved 2,613 patients judged to have a low risk of death at the time of enrollment. The 28-day mortality rate from all causes was 17% on placebo vs. 18.5% on APC, relative risk 1.08, 95% confidence interval 0.92–1.28 (116). Again, debate focused on subgroup analyses; analyses were restricted to small subgroups of patients with APACHE II score >25 or more than one organ failure, which failed to show benefit. However, these patient groups also had a lower mortality than in PROWESS.

Relative risk reduction of death was numerically lower in the subgroup of patients with recent surgery (n = 502) in the PROWESS trial (30.7% placebo vs. 27.8% APC) (119) when compared with the overall study population (30.8% placebo vs. 24.7% APC) (115). In the ADDRESS trial, patients with recent surgery and single organ dysfunction who received APC had significantly higher 28-day mortality rates (20.7% vs. 14.1%, $p = .03$, n = 635) (116).

Serious adverse events did not differ in the studies (115–117) with the exception of serious bleeding, which occurred more often in the patients treated with APC: 2% vs. 3.5% (PROWESS; $p = .06$) (115); 2.2% vs. 3.9% (ADDRESS; $p < .01$) (116); 6.5% (ENHANCE, open label) (117). The pediatric trial and implications are discussed in the pediatric consideration section of this article. (Appendix C provides absolute contraindications to use of rhAPC and prescribing information for relative contraindications.)

Intracranial hemorrhage (ICH) occurred in the PROWESS trial in 0.1% (placebo) and 0.2% (APC) (not significant) (106); in the ADDRESS trial 0.4% (placebo) vs. 0.5 % (APC) (not significant) (116); and in ENHANCE 1.5% (108). Registry studies of rhAPC report higher bleeding rates than randomized controlled trials, suggesting that the risk of bleeding in actual practice may be greater

than reported in PROWESS and ADDRESS (120, 121).

The two RCTs in adult patients were methodologically strong and precise and provided direct evidence regarding death rates. The conclusions are limited, however, by inconsistency that is not adequately resolved by subgroup analyses (thus the designation of moderate-quality evidence). Results, however, consistently fail to show benefit for the subgroup of patients at lower risk of death and consistently show increases in serious bleeding. The RCT in pediatric severe sepsis failed to show benefit and has no important limitations. Thus, for low-risk and pediatric patients, we rate the evidence as high quality.

For adult use there is probable mortality reduction in patients with clinical assessment of high risk of death, most of whom will have APACHE II ≥25 or multiple organ failure. There is likely no benefit in patients with low risk of death, most of whom will have APACHE II <20 or single organ dysfunction. The effects in patients with more than one organ failure but APACHE II <25 are unclear, and in that circumstance one may use clinical assessment of the risk of death and number of organ failures to support decision. There is a certain increased risk of bleeding with administration of rhAPC, which may be higher in surgical patients and in the context of invasive procedures. Decision on utilization depends on assessing likelihood of mortality reduction vs. increases in bleeding and cost. (Appendix D provides the nominal committee vote on recommendation for rhAPC.) A European regulatory mandated RCT of rhAPC vs. placebo in patients with septic shock is now ongoing (122).

J. Blood Product Administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis (see recommendations for initial resuscitation), we recommend that red blood cell transfusion occur when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin of 7.0–9.0 g/dL (70–90 g/L) in adults (grade 1B).

Rationale. Although the optimum hemoglobin for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin of 7–9 g/dL (70–90 g/L) when compared with 10–12 g/dL (100–200 g/L) was not associated with increased mortality in adults (123). Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption (124–126). This transfusion threshold of 7 g/dL (70 g/L) contrasts with the early goal-directed resuscitation protocol that uses a target hematocrit of 30% in patients with low $Scvo_2$ (measured in superior vena cava) during the first 6 hrs of resuscitation of septic shock.

2. We recommend that erythropoietin not be used as a specific treatment of anemia associated with severe sepsis but may be used when septic patients have other accepted reasons for administration of erythropoietin, such as renal failure-induced compromise of red blood cell production (grade 1B).

Rationale. No specific information regarding erythropoietin use in septic patients is available, but clinical trials in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome (127, 128). The effect of erythropoietin in severe sepsis and septic shock would not be expected to be more beneficial than in other critical conditions. Patients with severe sepsis and septic shock may have coexisting conditions that do warrant use of erythropoietin.

3. 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).

Rationale. Although clinical studies have not assessed the impact of transfusion of fresh frozen plasma on outcomes in critically ill patients, professional organizations have recommended fresh frozen plasma for coagulopathy when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgical or invasive procedures (129–131). In addition, transfusion of fresh frozen plasma in nonbleeding patients with mild abnormalities of prothrombin time usually fails to correct the prothrombin time (132). There are no studies to suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.

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

Rationale. A phase III clinical trial of high-dose antithrombin did not demonstrate any beneficial effect on 28-day all-cause mortality in adults with severe sepsis and septic shock. High-dose antithrombin was associated with an increased risk of bleeding when administered with heparin (133). Although a *post hoc* subgroup analysis of patients with severe sepsis and high risk of death showed better survival in patients receiving antithrombin, antithrombin cannot be recommended until further clinical trials are performed (134).

5. In patients with severe sepsis, we suggest that platelets be administered when counts are $<5000/mm^3$ (5×10^9/L) regardless of apparent bleeding. Platelet transfusion may be considered when counts are $5000–30{,}000/mm^3$ ($5–30 \times 10^9$/L) and there is a significant risk of bleeding. Higher platelet counts ($\geq 50{,}000/mm^3$ [50×10^9/L]) are typically required for surgery or invasive procedures (grade 2D).

Rationale. Guidelines for transfusion of platelets are derived from consensus opinion and experience in patients undergoing chemotherapy. Recommendations take into account the etiology of thrombocytopenia, platelet dysfunction, risk of bleeding, and presence of concomitant disorders (129, 131).

II. SUPPORTIVE THERAPY OF SEVERE SEPSIS

A. Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS)

1. We recommend that clinicians target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (grade 1B).
2. We recommend that plateau pressures be measured in patients with ALI/ARDS and that the initial upper limit goal for plateau pressures in a passively inflated patient be ≤30 cm H_2O. Chest wall compliance should be considered in the assessment of plateau pressure (grade 1C).

Rationale. Over the past 10 yrs, several multicenter randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume (135–139). These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups (135, 140). The largest trial of a volume- and pressure-limited strategy showed a 9% decrease of all-cause mortality in patients with ALI or ARDS ventilated with tidal volumes of 6 mL/kg of predicted body weight (PBW), as opposed to 12 mL/kg, and aiming for a plateau pressure ≤30 cm H_2O (135). The use of lung-protective strategies for patients with ALI is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ALI may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure chosen, the compliance of the thoracoabdominal compartment, and the vigor of the patient's breathing effort. Some clinicians believe it may be safe to ventilate with tidal volumes >6 mL/kg PBW as long as the plateau pressure can be maintained ≤30 cm H_2O (141, 142). The validity of this ceiling value will depend on breathing effort, as those who are actively inspiring generate higher transalveolar pressures for a given plateau pressure than those who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures >30 cm H_2O to meet vital clinical objectives. One retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤30 cm H_2O (143). An additional observational study suggested that knowledge of the plateau pressures was associated with lower plateau pressures; however, in that trial plateau pressure was not independently associated with mortality rates across a wide range of plateau pressures that bracketed 30 cm H_2O (144). The largest clinical trial employing a lung-protective strategy coupled limited pressure with limited tidal volumes to demonstrate a mortality benefit (135).

High tidal volumes that are coupled with high plateau pressures should be avoided in ALI/ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1–2 hrs from its initial value toward the goal of a "low" tidal volume (≈6 mL/kg PBW) achieved in conjunction with an end-inspiratory plateau pressure ≤30 cm H_2O. If plateau pressure remains >30 after reduction of tidal volume to 6 mL/kg PBW, tidal volume should be reduced further to as low as 4 mL/kg PBW. (Appendix E provides ARDSNet ventilator management and formulas to calculate predicted body weight.)

No single mode of ventilation (pressure control, volume control, airway pressure release ventilation, high-frequency ventilation) has been consistently shown advantageous when compared with any other that respects the same principles of lung protection.

3. We recommend that hypercapnia (allowing $Paco_2$ to increase above its premorbid baseline, so-called permissive hypercapnia) be allowed in patients with ALI/ARDS if needed to minimize plateau pressures and tidal volumes (grade 1C).

Rationale. An acutely elevated $Paco_2$ may have physiologic consequences that include vasodilation as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series (145, 146). Patients treated in larger trials that have the goal of limiting tidal volumes and airway pressures have demonstrated improved outcomes, but permissive hypercapnia was not a primary treatment goal in these studies (135). The use of hypercapnia is limited in patients with preexisting metabolic acidosis and is contraindicated in patients with increased intracranial pressure. Sodium bicarbonate or tromethamine (THAM) infusion may be considered in selected patients to facilitate use of permissive hypercarbia (147, 148).

4. We recommend that positive end-expiratory pressure (PEEP) be set so as to avoid extensive lung collapse at end-expiration (grade 1C).

Rationale. Raising PEEP in ALI/ARDS keeps lung units open to participate in gas exchange. This will increase Pao_2 when PEEP is applied through either an endotracheal tube or a face mask (149–151). In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury when relatively high plateau pressures are in use. One large multicenter trial of the protocol-driven use of higher PEEP in conjunction with low tidal volumes did not show benefit or harm when compared with lower PEEP levels (152). Neither the control nor experimental group in that study, however, was clearly exposed to hazardous plateau pressures. A recent multicenter Spanish trial compared a high PEEP, low-moderate tidal volume approach to one that used conventional tidal volumes and the least PEEP achieving adequate oxygenation. A marked survival advantage favored the former approach in high-acuity patients with ARDS (153). Two options are recommended for PEEP titration. One option is to titrate PEEP (and tidal volume) according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance, reflecting a favorable balance of lung recruitment and overdistension (154). The second option is to titrate PEEP based on severity of oxygenation deficit and guided by the Fio_2 required to maintain adequate oxygenation (135) (Appendix D). Whichever the indicator—compliance or oxygenation—recruiting maneuvers are reasonable to employ in the process of PEEP selection. Blood pressure and oxygenation should be monitored and recruitment discontinued if deterioration in these variables is observed. A PEEP >5 cm H_20 is usually required to avoid lung collapse (155).

5. We suggest prone positioning in ARDS patients requiring potentially injurious levels of Fio_2 or plateau pressure who are not at high risk for adverse consequences of positional changes in facilities that have experience with such practices (grade 2C).

Rationale. Several small studies and one larger study have shown that a majority of patients with ALI/ARDS respond to the prone position with improved oxygenation (156–159). One large multicenter trial of prone positioning for approximately 7 hrs/day did not show improvement in mortality rates in patients with ALI/ARDS; however, a *post hoc* analysis suggested improvement in those patients with the most severe hypoxemia by Pao_2/Fio_2 ratio, in those exposed to high tidal volumes, and in those who improved CO_2 exchange as a result of proning (159). A second large trial of prone positioning, conducted for an average of approximately 8 hrs/day for 4 days in adults with hypoxemic respiratory failure of low-moderate acuity, confirmed improvement in oxygenation but also failed to show a survival advantage (160). However, a randomized study that extended the length of time for

proning each day to a mean of 17 hrs for a mean of 10 days supported benefit of proning, with randomization to supine position an independent risk factor for mortality by multivariate analysis (161). Prone positioning may be associated with potentially life-threatening complications, including accidental dislodgment of the endotracheal tube and central venous catheters, but these complications can usually be avoided with proper precautions.

6a. Unless contraindicated, we recommend that mechanically ventilated patients be maintained with the head of the bed elevated to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).

6b. We suggest that the head of bed be elevated approximately 30–45° (grade 2C).

Rationale. The semirecumbent position has been demonstrated to decrease the incidence of ventilator-associated pneumonia (VAP) (162). Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed enterally in the supine position developed VAP (163). However, the bed position was only monitored once a day, and patients who did not achieve the desired bed elevation were not included in the analysis (163). A recent study did not show a difference in incidence of VAP between patients maintained in supine and semirecumbent positions (164). In this study, patients in the semirecumbent position did not consistently achieve the desired head of the bed elevation, and the head of bed elevation in the supine group approached that of the semirecumbent group by day 7 (164). When necessary, patients may be laid flat for procedures, hemodynamic measurements, and during episodes of hypotension. Patients should not be fed enterally with the head of the bed at 0°.

7. We suggest that noninvasive mask ventilation (NIV) only be considered in that minority of ALI/ARDS patients with mild-moderate hypoxemic respiratory failure (responsive to relatively low levels of pressure support and PEEP) with stable hemodynamics who can be made comfortable and are easily arousable; who are able to protect the airway and spontaneously clear the airway of secretions; and who are anticipated to recover rapidly from the precipitating insult. A low threshold for airway intubation should be maintained (grade 2B).

Rationale. Obviating the need for airway intubation confers multiple advantages: better communication, lower incidence of infection, reduced requirements for sedation. Two RCTs demonstrate improved outcome with the use of NIV when it can be employed successfully (162, 165). Unfortunately, only a small percentage of patients with life-threatening hypoxemia can be managed in this way.

8. We recommend that a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) They are arousable; b) they are hemodynamically stable (without vasopressor agents); c) they have no new potentially serious conditions; d) they have low ventilatory and end-expiratory pressure requirements; and e) their F_{IO_2} requirements could be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (Appendix E). Spontaneous breathing trial options include a low level of pressure support, continuous positive airway pressure (≈5 cm H_2O), or a T-piece (grade 1A).

Rationale. Recent studies demonstrate that daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation (166–169). Successful completion of spontaneous breathing trials leads to a high likelihood of successful discontinuation of mechanical ventilation.

9. We recommend against the routine use of the pulmonary artery catheter for patients with ALI/ARDS (grade 1A).

Rationale. While insertion of a pulmonary artery catheter may provide useful information on a patient's volume status and cardiac function, potential benefits of such information may be confounded by differences in interpretation of results (170–172), lack of correlation of pulmonary artery occlusion pressures with clinical response (173), and absence of a proven strategy to use catheter results to improve patient outcomes (174). Two multicenter randomized trials, one in patients with shock or acute lung injury (175) and one in patients with acute lung injury (176), failed to show benefit with the routine use of pulmonary artery catheters in patients with acute lung injury. In addition, other studies in different types of critically ill patients have failed to show definitive benefit with routine use of the pulmonary artery catheter (177–179). 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.

10. To decrease days of mechanical ventilation and ICU length of stay we recommend a conservative fluid strategy for patients with established acute lung injury who do not have evidence of tissue hypoperfusion (grade 1C).

Rationale. Mechanisms for the development of pulmonary edema in patients with acute lung injury include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure (180, 181). Small prospective studies in patients with critical illness and acute lung injury have suggested that less weight gain is associated with improved oxygenation (182) and fewer days of mechanical ventilation (183, 184). Use of a fluid-conservative strategy directed at minimizing fluid infusion and weight gain in patients with acute lung injury based on either a central venous catheter or a pulmonary artery catheter along with clinical variables to guide treatment strategies led to fewer days of mechanical ventilation and reduced length of ICU stay without altering the incidence of renal failure or mortality rates (185). Of note, this strategy was only used in patients with established acute lung injury, some of whom had shock present. Active attempts to reduce fluid volume were conducted only during periods free from shock.

B. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. We recommend sedation protocols with a sedation goal when sedation of critically ill mechanically ventilated patients with sepsis is required (grade 1B).

Rationale. A growing body of evidence indicates that the use of protocols for

sedation of critically ill ventilated patients can reduce the duration of mechanical ventilation and ICU and hospital length of stay (186–188). A randomized, controlled clinical trial found that protocol use reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates (186).

A report describing the implementation of protocols, including sedation and analgesia, using a short-cycle improvement methodology in the management of critically ill patients demonstrated a decrease in the cost per patient-day and a decrease of ICU length of stay (187). Furthermore, a prospective before-and-after study on the implementation of a sedation protocol demonstrated enhanced quality of sedation with reduced drug costs. Although this protocol also may have contributed to a longer duration of mechanical ventilation, ICU discharge was not delayed (188). Despite the lack of evidence regarding the use of subjective methods of evaluation of sedation in septic patients, the use of a sedation goal has been shown to decrease the duration of mechanical ventilation in critically ill patients (186). Several subjective sedation scales have been described in the medical literature. Currently, however, there is not a clearly superior sedation evaluation methodology against which these sedation scales can be evaluated (189). The benefits of sedation protocols appear to outweigh the risks.

2. We recommend intermittent bolus sedation or continuous infusion sedation to predetermined end points (e.g., sedation scales) with daily interruption/lightening of continuous infusion sedation with awakening and retitration if necessary for sedation administration to septic mechanically ventilated patients (grade 1B).

Rationale. Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily interruption, and retitration or systemic titration to a predefined end point have been demonstrated to decrease the duration of mechanical ventilation (186, 189, 190). Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because neuromuscular blocking drugs must also be discontinued in that situation. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined. An observational study of mechanically ventilated patients showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital length of stay (191).

Similarly, a prospective, controlled study in 128 mechanically ventilated adults receiving continuous intravenous sedation demonstrated that a daily interruption in the continuous sedative infusion until the patient was awake decreased the duration of mechanical ventilation and ICU length of stay (192). Although the patients did receive continuous sedative infusions in this study, the daily interruption and awakening allowed for titration of sedation, in effect making the dosing intermittent. Systematic (protocolized) titration to a predefined end point has also been shown to alter outcome (186). Additionally, a randomized prospective blinded observational study demonstrated that although myocardial ischemia is common in critically ill ventilated patients, daily sedative interruption is not associated with an increased occurrence of myocardial ischemia (193). Thus, the benefits of daily interruption of sedation appear to outweigh the risks. These benefits include potentially shorter duration of mechanical ventilation and ICU stay, better assessment of neurologic function, and reduced costs.

3. We recommend that NMBAs be avoided if possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with monitoring the depth of blockade with train-of-four monitoring should be used (grade 1B).

Rationale. Although NMBAs are often administered to critically ill patients, their role in the ICU is not well defined. No evidence exists that maintaining neuromuscular blockade in this patient population reduces mortality or major morbidity. In addition, no studies have been published that specifically address the use of NMBAs in septic patients.

The most common indication for NMBA use in the ICU is to facilitate mechanical ventilation (194). When appropriately used, NMBAs may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures (195). Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow (196). However, a randomized, placebo-controlled clinical trial in patients with severe sepsis demonstrated that oxygen delivery, oxygen consumption, and gastric intramucosal pH were not improved during profound neuromuscular blockade (197).

An association between NMBA use and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population (195, 198–201). The mechanisms by which NMBAs produced or contribute to myopathies and neuropathies in critically ill patients are presently unknown. There appears to be an added association with the concurrent use of NMBAs and steroids. Although no studies exist specific to the septic patient population, it seems clinically prudent based on existent knowledge that NMBAs not be administered unless there is a clear indication for neuromuscular blockade that cannot be safely achieved with appropriate sedation and analgesia (195).

Only one prospective, randomized clinical trial has evaluated peripheral nerve stimulation vs. standard clinical assessment in ICU patients. Rudis et al. (202) randomized 77 critically ill patients requiring neuromuscular blockade in the ICU to receive dosing of vecuronium based on train-of-four stimulation or clinical assessment (control). The peripheral nerve stimulation group received less drug and recovered neuromuscular function and spontaneous ventilation faster than the control group. Nonrandomized observational studies have suggested that peripheral nerve monitoring reduces or has no effect on clinical recovery from NMBAs in the ICU (203, 204).

Benefits to neuromuscular monitoring, including faster recovery of neuromuscular function and shorter intubation times, appear to exist. A potential for cost savings (reduced total dose of NMBAs and shorter intubation times) also may exist, although this has not been studied formally.

C. Glucose Control

1. We recommend that following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted to the ICU receive intravenous insulin therapy to reduce blood glucose levels (grade 1B).
2. We suggest use of a validated protocol for insulin dose adjustments and tar-

geting glucose levels to the <150 mg/dL range (grade 2C).
3. We recommend that all patients receiving intravenous insulin receive a glucose calorie source and that blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).
4. We recommend that low glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may overestimate arterial blood or plasma glucose values (grade 1B).

Rationale. The consensus on glucose control in severe sepsis was achieved at the first committee meeting and subsequently approved by the entire committee. (Appendix G presents the committee vote.) One large randomized single-center trial in a predominantly cardiac surgical ICU demonstrated a reduction in ICU mortality with intensive intravenous insulin (Leuven protocol) targeting blood glucose to 80–110 mg/dL (for all patients, a relative 43% and absolute 3.4% mortality reduction; for those with >5 days in the ICU, a 48% relative and 9.6% absolute mortality reduction) (205). A reduction in organ dysfunction and ICU length of stay (LOS) (from a median of 15 to 12 days) was also observed in the subset with ICU LOS >5 days. A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU LOS of >3 days in three medical ICUs (206). Overall mortality was not reduced, but ICU and hospital LOS were reduced associated with earlier weaning from mechanical ventilation and less acute kidney injury. In patients with a medical ICU LOS >3 days, hospital mortality was reduced with intensive insulin therapy (43% vs. 52.5%; $p = .009$). However, investigators were unsuccessful in predicting ICU LOS, and 433 patients (36%) had an ICU LOS of <3 days. Furthermore, use of the Leuven protocol in the medical ICU resulted in a nearly three-fold higher rate of hypoglycemia than in the original experience (18% vs. 6.2% of patients) (205, 206).

One large before-and-after observational trial showed a 29% relative and 6.1% absolute reduction in mortality and a 10.8% reduction in median ICU LOS (207). In a subgroup of 53 patients with septic shock, there was an absolute mortality reduction of 27% and a relative reduction of 45% ($p = .02$). Two additional observational studies reported an association of mean glucose levels with reductions in mortality, polyneuropathy, acute renal failure, nosocomial bacteremia, and number of transfusions, and they suggested that a glucose threshold for improved mortality lies somewhere between 145 and 180 mg/dL (208, 209). However, a large observational study (n = 7,049) suggested that both a lower mean glucose and less variation of blood glucose may be important (210). A meta-analysis of 35 trials on insulin therapy in critically ill patients, including 12 randomized trials, demonstrated a 15% reduction in short-term mortality (relative risk 0.85, 95% confidence interval 0.75–0.97) but did not include any studies of insulin therapy in medical ICUs (211).

Two additional multicenter RCTs of intensive insulin therapy, one focusing on patients with severe sepsis (VISEP) and the second on medical and surgical ICU patients, failed to demonstrate improvement in mortality but are not yet published (212, 213). Both were stopped earlier than planned because of high rates of hypoglycemia and adverse events in the intensive insulin groups. A large RCT that is planned to compare targeting 80–110 mg/dL (4.5–6.0 mmol/L) vs. 140–180 mg/dL (8–10 mmol/L) and recruit >6,000 patients (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, or NICE-SUGAR) is ongoing (214).

Several factors may affect the accuracy and reproducibility of point-of-care testing of blood capillary blood glucose, including the type and model of the device used, user expertise, and patient factors, including hematocrit (false elevation with anemia), Pao_2, and drugs (215). One report showed overestimation of arterial plasma glucose values by capillary point-of-care testing sufficient to result in different protocol-specified insulin dose titration. The disagreement between protocol-recommended insulin doses was largest when glucose values were low (216). A recent review of 12 published insulin infusion protocols for critically ill patients showed wide variability in insulin dose recommendations and variable glucose control during simulation (217). This lack of consensus about optimal dosing of intravenous insulin may reflect variability in patient factors (severity of illness, surgical vs. medical settings) or practice patterns (e.g., approaches to feeding, intravenous dextrose) in the environments in which these protocols were developed and tested. Alternatively, some protocols may be more effective than others. This conclusion is supported by the wide variability in hypoglycemia rates reported with protocols (205–207, 212, 213). Thus, the use of a validated and safe intensive insulin protocol is important not only for clinical care but also for the conduct of clinical trials to avoid hypoglycemia, adverse events, and premature termination of these trials before the efficacy signal, if any, can be determined.

The finding of reduced morbidity and mortality within the longer ICU length of stay subsets along with acceptable cost weighed heavily on our recommendation to attempt glucose control after initial stabilization of the patient with hyperglycemia and severe sepsis. However, the mortality benefit and safety of intensive insulin therapy (goal to normalize blood glucose) have been questioned by two recent trials, and we recommend maintaining glucose levels <150 mg/dL until recent and ongoing trials are published or completed. Further study of protocols that have been validated to be safe and effective for controlling blood glucose concentrations and blood glucose variation in the severe sepsis population is needed.

D. Renal Replacement

1. We suggest that continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).
2. We suggest the use of continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 2D).

Rationale. Although numerous nonrandomized studies have reported a nonsignificant trend toward improved survival using continuous methods (218–225), two meta-analyses (226, 227) reported the absence of significant difference in hospital mortality between patients who receive continuous and intermittent renal replacement therapies. This absence of apparent benefit of one modality over the other persists even when the analysis is restricted to only randomized studies (227). To date, five prospective randomized studies have been published (228–232). Four of them found no significant difference in mortality (229–232). One study found significantly higher

mortality in the continuous treatment group (228), but imbalanced randomization had led to a higher baseline severity of illness in this group. When a multivariable model was used to adjust for severity of illness, no difference in mortality was apparent between the groups (228). Most studies comparing modes of renal replacement in the critically ill have included a small number of patients and some major weaknesses (randomization failure, modifications of therapeutic protocol during the study period, combination of different types of continuous renal replacement therapies, small number of heterogenous groups of patients enrolled). The most recent and largest randomized study (232) enrolled 360 patients and found no significant difference in survival between the two groups. Moreover, there is no current evidence to support the use of continuous therapies in sepsis independent of renal replacement needs.

Concerning the hemodynamic tolerance of each method, no current evidence exists to support a better tolerance with continuous treatments. Only two prospective studies (230, 233) have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion (233) and no survival benefit (230). Four other prospective studies did not find any significant difference in mean arterial pressure or drop in systolic pressure between the two methods (229, 231, 232, 234). Concerning fluid balance management, two studies reported a significant improvement in goal achievement with continuous methods (228, 230). In summary, current evidence is insufficient to draw strong conclusions regarding the mode of replacement therapy for acute renal failure in septic patients.

Four randomized controlled trials have addressed whether the dose of continuous renal replacement affects outcomes in patients with acute renal failure (235–238). Three found improved mortality in patients receiving higher doses of renal replacement (235, 237, 238), while one (236) did not. None of these trials was conducted specifically in patients with sepsis. Although the weight of current evidence suggests that higher doses of renal replacement may be associated with improved outcomes, these results may not be easily generalizable. The results of two very large multicenter randomized trials comparing the dose of renal replacement (ATN in the United States and RENAL in Australia and New Zealand) will be available in 2008 and will greatly inform practice.

E. Bicarbonate Therapy

1. We recommend against the use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH $\geq$7.15 (grade 1B).

Rationale. No evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidemia associated with sepsis. Two randomized, blinded, crossover studies that compared equimolar saline and bicarbonate in patients with lactic acidosis failed to reveal any difference in hemodynamic variables or vasopressor requirements (239, 240). The number of patients with pH $<$7.15 in these studies was small. Bicarbonate administration has been associated with sodium and fluid overload, an increase in lactate and P_{CO_2}, and a decrease in serum ionized calcium, but the relevance of these variables to outcome is uncertain. The effect of bicarbonate administration on hemodynamics and vasopressor requirements at lower pH as well as the effect on clinical outcomes at any pH is unknown. No studies have examined the effect of bicarbonate administration on outcomes.

F. Deep Vein Thrombosis Prophylaxis

1. We recommend that patients with severe sepsis receive deep vein thrombosis (DVT) prophylaxis with either a) low-dose unfractionated heparin (UFH) administered twice or three times per day; or b) daily low-molecular weight heparin (LMWH) unless there are contraindications (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) (grade 1A).
2. We recommend that septic patients who have a contraindication for heparin use receive mechanical prophylactic device, such as graduated compression stockings or intermittent compression devices, unless contraindicated (grade 1A).
3. We suggest that in very high-risk patients, such as those who have severe sepsis and history of DVT, trauma, or orthopedic surgery, a combination of pharmacologic and mechanical therapy be used unless contraindicated or not practical (grade 2C).
4. We suggest that in patients at very high risk, LMWH be used rather than UFH as LMWH is proven superior in other high-risk patients (grade 2C).

Rationale. ICU patients are at risk for DVT (241). Significant evidence exists for benefit of DVT prophylaxis in ICU patients in general. No reasons suggest that severe sepsis patients would be different from the general patient population.

Nine randomized placebo-controlled clinical trials of DVT prophylaxis in general populations of acutely ill patients exist (242–250). All nine trials showed reduction in DVT or pulmonary embolism. The prevalence of infection/sepsis was 17% in all studies in which this was ascertainable, with a 52% prevalence of infection/sepsis patients in the study that included ICU patients only. Benefit of DVT prophylaxis is also supported by meta-analyses (251, 252). With that in mind, DVT prophylaxis would appear to have a high grade for quality of evidence (A). Because the risk of administration to the patient is small, the gravity of the potential result of not administering is great, and the cost is low, the grading of the strength of the recommendation is strong. The evidence supports equivalency of LMWH and UFH in general medical populations. A recent meta-analysis comparing UFH twice daily and three times daily demonstrated that UFH three times daily produced better efficacy and twice daily produced less bleeding (253). Practitioners should use underlying risk for VTE and bleeding to individualize choice of twice daily vs. three times daily.

The cost of LMWH is greater and the frequency of injection is less. UFH is preferred over LMWH in patients with moderate to severe renal dysfunction.

Mechanical methods (intermittent compression devices and graduated compression stockings) are recommended when anticoagulation is contraindicated or as an adjunct to anticoagulation in very high-risk patients (254–256). In very high-risk patients, LMWH is preferred over UFH (257–259). Patients receiving heparin should be monitored for development of heparin-induced thrombocytopenia.

G. Stress Ulcer Prophylaxis

1. We recommend that stress ulcer prophylaxis using H2 blocker (grade 1A) or proton pump inhibitor (grade 1B) be given to patients with severe sepsis

to prevent upper gastrointestinal (GI) bleed. The benefit of prevention of upper GI bleed must be weighed against the potential effect of an increased stomach pH on development of ventilator-associated pneumonia.

Rationale. Although no study has been performed specifically in patients with severe sepsis, trials confirming the benefit of stress ulcer prophylaxis in reducing upper GI bleeds in general ICU populations would suggest that 20% to 25% of patients enrolled in these types of trials have sepsis (260–263). This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the conditions shown to benefit from stress ulcer prophylaxis (coagulopathy, mechanical ventilation, hypotension) are frequently present in patients with severe sepsis and septic shock (264, 265).

Although there are individual trials that have not shown benefit from stress ulcer prophylaxis, numerous trials and a meta-analysis show reduction in clinically significant upper GI bleeding, which we consider significant even in the absence of proven mortality benefit (266–269). The benefit of prevention of upper GI bleed must be weighed against the potential effect of increased stomach pH on greater incidence of ventilator-associated pneumonia (270). Those severe sepsis patients with the greatest risk of upper GI bleeding are likely to benefit most from stress ulcer prophylaxis. The rationale for preferring suppression of acid production over sulcrafate was based on the study of 1,200 patients by Cook et al. (271, 272) comparing H2 blockers and sulcrafate and a meta-analysis. Two studies support equivalency between H2 blockers and proton pump inhibitors. One study included very ill ICU patients; the second study was larger and demonstrated noninferiority of omeprazole suspension for clinically significant stress ulcer bleeding (273, 274). No data relating to utility of enteral feeding in stress ulcer prophylaxis exist. Patients should be periodically evaluated for continued need for prophylaxis.

H. Selective Digestive Tract Decontamination (SDD)

The guidelines group was evenly split on the issue of SDD, with equal numbers weakly in favor and against recommending the use of SDD (Appendix H). The committee therefore chose not to make a recommendation for the use of SDD specifically in severe sepsis at this time. The final consensus on use of SDD in severe sepsis was achieved at the last nominal committee meeting and subsequently approved by the entire committee (Appendix H provides the committee vote).

Rationale. The cumulative conclusion from the literature demonstrates that prophylactic use of SDD (enteral nonabsorbable antimicrobials and short-course intravenous antibiotics) reduces infections, mainly pneumonia, and mortality in the general population of critically ill and trauma patients (275–286) without promoting emergence of resistant Gram-negative bacteria. *Post hoc* subgroup analyses (287, 288) of two prospective blinded studies (289, 290) suggest that SDD reduces nosocomial (secondary) infections in ICU patients admitted with primary infections (268) and may reduce mortality (288). No studies of SDD specifically focused on patients with severe sepsis or septic shock. The use of SDD in severe sepsis patients would be targeted toward preventing secondary infection. As the main effect of SDD is in preventing ventilator-associated pneumonia (VAP), studies comparing SDD with nonantimicrobial interventions, such as ventilator bundles for reducing VAP, are needed. Further investigation is required to determine the comparative efficacy of these two interventions, separately or in combination. Although studies incorporating enteral vancomycin in the regimen appear to be safe (291–293), concerns persist about the potential for emergence of resistant Gram-positive infections.

I. Consideration for Limitation of Support

1. 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).

Rationale. Decisions for less aggressive support or withdrawal of support may be in the patient's best interest (294–296). Too frequently, inadequate physician/family communication characterizes end-of-life care in the ICU. The level of life support given to ICU patients may not be consistent with their wishes. Early and frequent caregiver discussions with patients who face death in the ICU and with their loved ones may facilitate appropriate application and withdrawal of life-sustaining therapies. A recent RCT demonstrated reduction of anxiety and depression in family members when end-of-life meetings were carefully planned and conducted, included advance care planning, and provided relevant information about diagnosis, prognosis, and treatment (297).

III. Pediatric Considerations in Severe Sepsis

While sepsis in children is a major cause of mortality, the overall mortality from severe sepsis in children is much lower that that in adults, estimated at about 10% (298). The definitions for severe sepsis and septic shock in children are similar but not identical to the definitions in adults (299). In addition to age-appropriate differences in vital signs, the definition of systemic inflammatory response syndrome requires the presence of either temperature or leukocyte abnormalities. The presence of severe sepsis requires sepsis plus cardiovascular dysfunction *or* ARDS *or* two or more other organ dysfunctions (299).

A. Antibiotics

1. We recommend that antibiotics be administered within 1 hr of the identification of severe sepsis, after appropriate cultures have been obtained (grade 1D).

Early antibiotic therapy is as critical for children with severe sepsis as it is for adults.

B. Mechanical Ventilation

No graded recommendations.

Due to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation (300). Drugs used for intubation have important side effects in these patients; for example, concerns have been raised about the safety of using etomidate in children with meningococcal sepsis because of adrenal suppression effect (301). The principles of lung-protective strategies are applied to children as they are to adults.

C. Fluid Resuscitation

1. We suggest that initial resuscitation begin with infusion of crystalloids with boluses of 20 mL/kg over 5–10 mins, titrated to clinical monitors of cardiac output, including heart rate,

urine output, capillary refill, and level of consciousness (grade 2C).

Intravenous access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in children than in adults. The American Heart Association and the American Academy of Pediatrics have developed pediatric advanced life support guidelines for emergency establishment of intravascular support encouraging early intraosseous access (302). On the basis of a number of studies, it is accepted that aggressive fluid resuscitation with crystalloids or colloids is of fundamental importance to survival of septic shock in children (303–308). Three randomized controlled trials compared the use of colloid to crystalloid resuscitation in children with dengue shock (303, 307, 308). No difference in mortality between colloid or crystalloid resuscitation was shown.

Children normally have a lower blood pressure than adults, and fall in blood pressure can be prevented by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of adequacy of fluid resuscitation. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 mL/kg but can be much higher (304–308). However, the rate of fluid administration should be reduced substantially when there are (clinical) signs of adequate cardiac filling without hemodynamic improvement.

D. Vasopressors/Inotropes (Should Be Used in Volume-Loaded Patients With Fluid Refractory Shock)

1. We suggest dopamine as the first choice of support for the pediatric patient with hypotension refractory to fluid resuscitation (grade 2C).

In the initial resuscitation phase, vasopressor therapy may be required to sustain perfusion pressure, even when hypovolemia has not yet been resolved. Children with severe sepsis can present with low cardiac output and high systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance shock. At various stages of sepsis or the treatment thereof, a child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the clinical state of the child.

Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion (309).

2. We suggest that patients with low cardiac output and elevated systemic vascular resistance states (cool extremities, prolonged capillary refill, decreased urine output but normal blood pressure following fluid resuscitation) be given dobutamine (grade 2C).

The choice of vasoactive agent is determined by the clinical examination. For the child with a persistent low cardiac output state with high systemic vascular resistance despite fluid resuscitation and inotropic support, vasodilator therapy may reverse shock (310). When pediatric patients remain in a normotensive low cardiac output and high vascular resistance state despite epinephrine and vasodilator therapy, the use of a phosphodiesterase inhibitor may be considered (311–313). In the case of extremely low systemic vascular resistance despite the use of norepinephrine, vasopressin use has been described in a number of case reports. There is no clear evidence for the use of vasopressin in pediatric sepsis (314, 315).

E. Therapeutic End Points

1. We suggest that the therapeutic end points of resuscitation of septic shock be normalization of the heart rate, capillary refill of <2 secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL·kg^{-1}·hr^{-1}, and normal mental status (290) (grade 2C).

Capillary refill may be less reliable in a cold environment. Other end points that have been widely used in adults and may logically apply to children include decreased lactate and improved base deficit, $Scvo_2 \geq 70\%$ or $S\bar{V}o_2 \geq 65\%$, central venous pressure of 8–12 mm Hg, or other methods to analyze cardiac filling. Optimizing preload optimizes cardiac index. In terms of identifying acceptable cardiac output in children with systemic arterial hypoxemia, such as cyanotic congenital heart disease or severe pulmonary disease, arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation with oxygen. As noted previously, blood pressure by itself is not a reliable end point for resuscitation. If a thermodilution catheter is used, therapeutic end points are cardiac index >3.3 and <6.0 L·min^{-1}·m^{-2} with normal coronary perfusion pressure (mean arterial pressure minus central venous pressure) for age (290). Using clinical end points, such as reversal of hypotension and restoration of capillary refill, for initial resuscitation at the community hospital level before transfer to a tertiary center was associated with significantly improved survival rates in children with septic shock (305). Development of a transport system including publicizing to local hospitals and transport with mobile intensive care services significantly decreased the case fatality rate from meningococcal disease in the United Kingdom (316).

F. Approach to Pediatric Septic Shock

Figure 1 shows a flow diagram summarizing an approach to pediatric septic shock (317).

G. Steroids

1. We suggest that hydrocortisone therapy be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency (grade 2C).

Patients at risk for adrenal insufficiency include children with severe septic shock and purpura (318, 319), children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. Children who have clear risk factors for adrenal insufficiency should be treated with stress-dose steroids (hydrocortisone 50 mg/m^2/24 hrs).

Adrenal insufficiency in pediatric severe sepsis is associated with a poor prognosis (320). No strict definitions exist, but absolute adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol concentration <18 μg/dL (496 nmol/L). A post 30- or 60-min ACTH stimulation test increase in cortisol of ≤ 9 μg/dL (248 mmol/L) has been used to define relative adrenal insufficiency. The treatment of relative adrenal insufficiency in children with septic shock is controversial. A retrospective study from a large administrative database recently

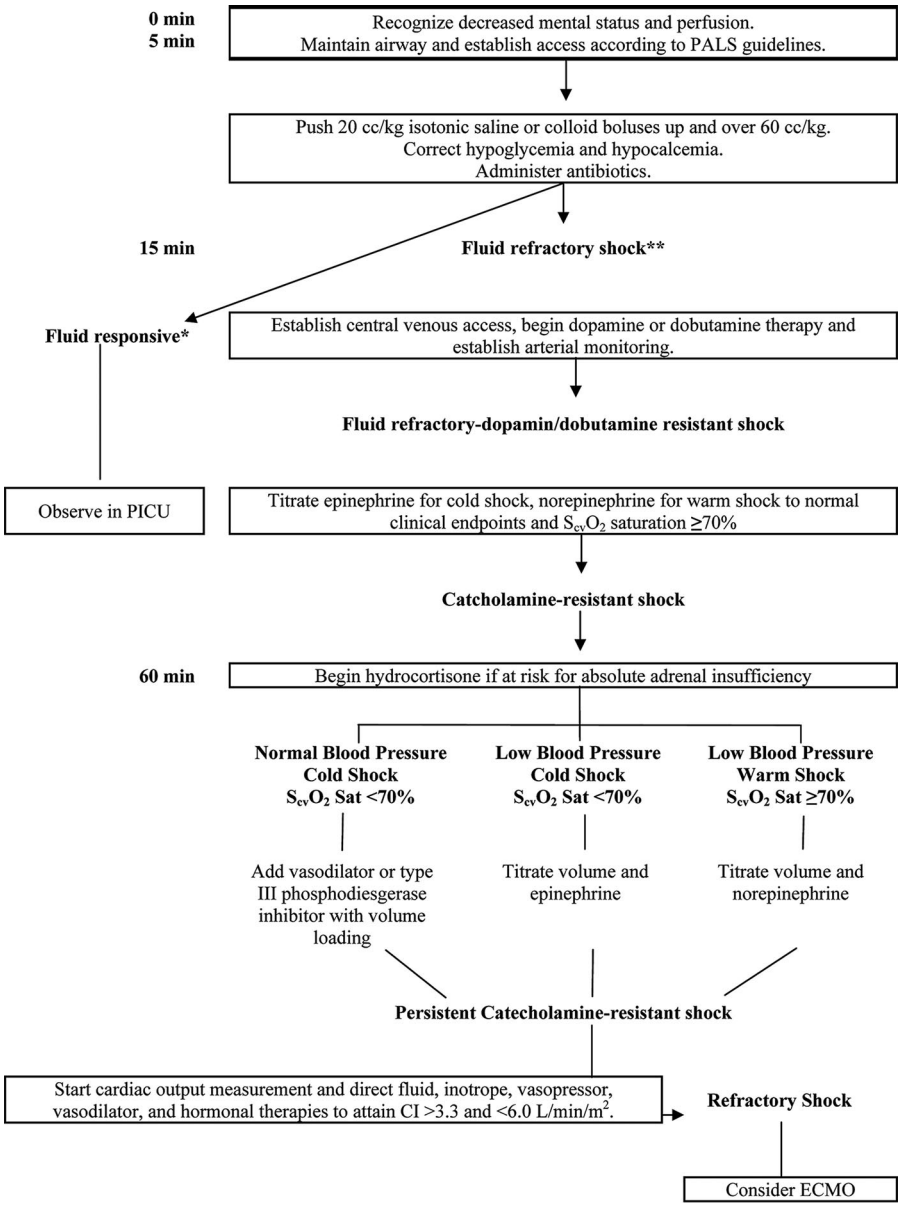

Figure 1. Approach to pediatric shock. *Normalization of blood pressure and tissue perfusion; **hypotension, abnormal capillary refill or extremity coolness. *PALS,* Pediatric Advanced Life Support; *PICU,* pediatric intensive care unit; *CI,* cardiac index; ECMO, extracorporeal membrane oxygenation.

reported that the use of any corticosteroids in children with severe sepsis was associated with increased mortality (odds ratio 1.9, 95% confidence interval 1.7–2.2) (321). While steroids may have been given preferentially to more severely ill children, the use of steroids was an independent predictor of mortality in multivariable analysis (321). Given the lack of data in children and potential risk, steroids should not be used in children who do not meet minimal criteria for adrenal insufficiency. A randomized, controlled trial in children with septic shock is very much needed.

H. Protein C and Activated Protein C

1. We recommend against the use rhAPC in children (grade 1B).

Protein C concentrations in children reach adult values at the age of 3 yrs. This might indicate that the importance of protein C supplementation either as protein C concentrate or as rhAPC is even greater in young children than in adults (322). There has been one dose-finding, randomized, placebo-controlled study performed using protein C concentrate. This study was not powered to show an effect on mortality rate but did show a positive effect on sepsis-induced coagulation disturbances (323). An RCT of rhAPC in pediatric severe sepsis patients was stopped by recommendation of the Data Monitoring Committee for futility after enrollment of 399 patients: 28-day all cause mortality was 18% placebo group vs. 17% APC group. Major amputations occurred in 3% of the placebo group vs. 2% in the APC group (324). Due to the increased risk of bleeding (7% vs. 6% in the pediatric trial) and lack of proof of efficacy, rhAPC is not recommended for use in children.

I. DVT Prophylaxis

1. We suggest the use of DVT prophylaxis in postpubertal children with severe sepsis (grade 2C).

Most DVTs in young children are associated with central venous catheters. Femoral venous catheters are commonly used in children, and central venous catheter-associated DVTs occur in approximately 25% of children with a femoral central venous catheter. Heparin-bonded catheters may decrease the risk of catheter-associated DVT and should be considered for use in children with severe sepsis (325, 326). No data on the efficacy of UFH or LMWH prophylaxis to prevent catheter-related DVT in children in the ICU exist.

J. Stress Ulcer Prophylaxis

No graded recommendations.

Studies have shown that the rate of clinically important gastrointestinal bleeding in children occurs at rates similar to adults (327, 328). As in adults, coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding. Stress ulcer prophylaxis strategy is commonly used in mechanically ventilated children, usually with H2 blockers. Its effect is not known.

K. Renal Replacement Therapy

No graded recommendations.

Continuous veno-venous hemofiltration (CVVH) may be clinically useful in children with anuria/severe oliguria and fluid overload, but no large RCTs have been performed comparing CVVH with intermittent dialysis. A retrospective study of 113 critically ill children reported that children with less fluid overload before CVVH had better survival, especially in those children

with dysfunction of three or more organs (329). CVVH or other renal replacement therapy should be instituted in children with anuria/severe oliguria before significant fluid overload occurs.

L. Glycemic Control

No graded recommendations.

In general, infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4–6 $mg \cdot kg^{-1} \cdot min^{-1}$ or maintenance fluid intake with glucose 10%/NaCl-containing solution is advised. Associations have been reported between hyperglycemia and an increased risk of death and longer length of stay (330). A recent retrospective pediatric ICU study reported associations of hyperglycemia, hypoglycemia, and glucose variability with length of stay and mortality rates (331). No studies in pediatric patients (without diabetes mellitus) analyzing the effect of strict glycemic control using insulin exist. In adults, the recommendation is to maintain serum glucose <150 mg/dL. Insulin therapy to avoid long periods of hyperglycemia seems sensible in children as well, but the optimal goal glucose is not known. However, continuous insulin therapy should only be conducted with frequent glucose monitoring in view of the risks for hypoglycemia.

M. Sedation/Analgesia

1. We recommend sedation protocols with a sedation goal when sedation of critically ill mechanically ventilated patients with sepsis is required (grade 1D).

Appropriate sedation and analgesia are the standard of care for children who are mechanically ventilated. Although there are no data supporting any particular drugs or regimens, it should be noted that propofol should not be used for long-term sedation in children because of the reported association with fatal metabolic acidosis (332, 333).

N. Blood Products

No graded recommendations.

The optimal hemoglobin for a critically ill child with severe sepsis is not known. A recent multicenter trial reported similar outcomes in stable critically ill children managed with a transfusion threshold of 7 g/dL compared with those managed with a transfusion threshold of 9.5 g/dL (334). Whether a lower transfusion trigger is safe or appropriate in the initial resuscitation of septic shock has not been determined.

O. Intravenous Immunoglobulin

1. We suggest that immunoglobulin be considered in children with severe sepsis (grade 2C).

Administration of polyclonal intravenous immunoglobulin has been reported to reduce mortality rate and is a promising adjuvant in the treatment of sepsis and septic shock in neonates. A recent randomized controlled study of polyclonal immunoglobulin in pediatric sepsis syndrome patients (n = 100) showed a significant reduction in mortality and LOS and less progress to complications, especially disseminated intravascular coagulation (335).

P. Extracorporeal Membrane Oxygenation (ECMO)

1. We suggest that use of ECMO be limited to refractory pediatric septic shock and/or respiratory failure that cannot be supported by conventional therapies (grade 2C).

ECMO has been used in septic shock in children, but its impact is not clear. Survival from refractory shock or respiratory failure associated with sepsis is 80% in neonates and 50% in children. In one study analyzing 12 patients with meningococcal sepsis in ECMO, eight of the 12 patients survived, with six leading functionally normal lives at a median of 1 yr (range, 4 months to 4 yrs) of follow-up. Children with sepsis on ECMO do not perform worse than children without sepsis at long-term follow-up (336, 337).

Although the pediatric considerations section of this article offers important information to the practicing pediatric clinician for the management of critically ill children with sepsis, the reader is referred to the reference list for more in-depth descriptions of appropriate management of pediatric septic patients.

SUMMARY AND FUTURE DIRECTIONS

Although this document is static, the optimum treatment of severe sepsis and septic shock is a dynamic and evolving process. New interventions will be proven and, as stated in the current recommendations, established interventions may need modification. This publication represents an ongoing process. The Surviving Sepsis Campaign and the consensus committee members are committed to updating the guidelines regularly as new interventions are tested and published.

Although evidence-based recommendations have been published frequently in the medical literature, documentation of impact on patient outcome is limited (338). However, there is growing evidence that protocol implementation associated with education and performance feedback does change clinician behavior and may improve outcomes and reduce costs in severe sepsis (20, 24, 25). Phase III of the Surviving Sepsis Campaign targets the implementation of a core set of the previous recommendations in hospital environments where change in behavior and clinical impact are being measured. The sepsis bundles were developed in collaboration with the Institute of Healthcare Improvement (339). Concurrent or retrospective chart review will identify and track changes in practice and clinical outcome. Software and software support are available at no cost in seven languages, allowing bedside data entry and allowing creation of regular reports for performance feedback. The SSC also offers significant program support and educational materials at no cost to the user (www.survivingsepsis.org).

Engendering evidence-based change in clinical practice through multifaceted strategies while auditing practice and providing feedback to healthcare practitioners is the key to improving outcomes in severe sepsis. Nowhere is this more evident than in the worldwide enthusiasm for phase III of the SSC, a performance improvement program using SSC guideline-based sepsis bundles. Using the guidelines as the basis, the bundles have established a global best practice for the management of critically ill patients with severe sepsis. As of November 2007, nearly 12,000 patients had been entered into the SSC central database, representing efforts of 239 hospitals in 17 countries. Changes in practice and potential effects on survival are being measured.

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APPENDIX A

Source Control

Source Control Technique	Examples
Drainage	Intra-abdominal abscess Thoracic empyema Septic arthritis
Debridement	Pyelonephritis, cholangitis Infected pancreatic necrosis Intestinal infarction Mediastinitis
Device removal	Infected vascular catheter Urinary catheter Infected intrauterine contraceptive device
Definitive control	Sigmoid resection for diverticulitis Cholecystectomy for gangrenous cholecystitis Amputation for clostridial myonecrosis

APPENDIX B

Steroids

Considerable difference of opinion existed among committee members as to the best option for the style of the recommendations for steroid use in septic shock. Some committee members argued for two recommendations and pointed to the two distinct patient populations of the French Trial (enrollment early in septic shock and blood pressure unresponsive to vasopressors) and the CORTICUS trial (enrollment allowed up to 72 hrs and did not target patients with blood pressure unresponsive to vasopressin), leading to two distinct results. Furthermore, a single recommendation suggested to some that this approach might lead to excessive use of steroids and increased incidence of superinfections, citing the sepsis and septic shock adverse events in the steroid-treated patients in the CORTICUS trial. Those who argued for one recommendation pointed to problems with two different recommendations that would require the bedside clinician to choose a time point for classification of one or the other as well as a distinct blood pressure cutoff with the potential for the blood pressure to vary over time. In addition, there are inadequate data to provide standardization of how much fluids and vasopressors should be in place to call the blood pressure unresponsive or poorly responsive. These members also pointed to the fact that the increased superinfection/sepsis/septic shock adverse events in CORTICUS are contrary to the results of other stress-dose steroid trials, such as early ARDS (lower incidence of infections) (341), late ARDS (decreased development of septic shock), and community-acquired pneumonia (decreased development of septic shock) (114). Based on GRADE adjudication guidelines, a secret ballot vote was conducted to resolve the issue.

The two options put to vote were:

Two-Recommendation Option

1. We suggest that intravenous hydrocortisone be given to adult septic shock patients if blood pressure is inadequate with appropriate fluid resuscitation and vasopressor therapy (grade 2B).
2. We suggest intravenous hydrocortisone not be given to adult septic shock patients if blood pressure is adequate with appropriate fluid resuscitation and vasopressor therapy (grade 2B).

One-Recommendation Option

1. We suggest that intravenous hydrocortisone be given only to adult septic shock patients with blood pressure poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).

The committee vote that determined the current recommendation was:

Favor two-recommendation option—19
Favor one-recommendation option—31
Abstain—1

APPENDIX C

Contraindications to Use of Recombinant Human Activated Protein C (rhAPC)

rhAPC increases the risk of bleeding and is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

Active internal bleeding
Recent (within 3 months) hemorrhagic stroke
Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
Trauma with an increased risk of life-threatening bleeding
Presence of an epidural catheter
Intracranial neoplasm or mass lesion or evidence of cerebral herniation
Known hypersensitivity to rhAPC or any component of the product

See labeling instructions for relative contraindications. The committee recommends that platelet count be maintained at ≥30,000 during infusion of rhAPC. (*Physicians' Desk Reference, 61st Edition*. Montvale, NJ, Thompson PDR, 2007, p 1829).

APPENDIX D

Recombinant Activated Protein C Nominal Group Vote

Strong for use, 6
Weak for use, 15
Neutral, 1
Weak for not using, 0
Strong for not using, 0

APPENDIX E

ARDSNet Ventilator Management

Assist control mode—volume ventilation (96)
Reduce tidal volume to 6 mL/kg lean body weight
Keep inspiratory plateau pressure (Pplat) ≤30 cm H_2O
Reduce tidal volume as low as 4 mL/kg predicted body weight to limit Pplat
Maintain arterial oxygen saturation/pulse oximetry oxyhemoglobin saturation (Spo_2) 88% to 95%

Anticipated PEEP settings at various F_{IO_2} requirements
F_{IO_2} 0.3, 0.4, 0.4, 0.5, 0.5, 0.6, 0.7, 0.7, 0.7, 0.8, 0.9, 0.9, 0.9, 1.0
PEEP 5, 5, 8, 8, 10, 10, 10, 12, 14, 14, 14, 16, 18, 20–24

Predicted Body Weight Calculation
Male—50 + 2.3 (height [inches] − 60) or 50 + 0.91 (height [cm] − 152.4)
Female—45.5 + 2.3 (height [inches] − 60) or 45.5 + 0.91 (height [cm] − 152.4)

APPENDIX G

Glycemic Control Committee Vote

Glycemic control—90%
Total votes = 51
Agree—34
Too conservative, but accept—4
Too liberal, but accept—8
Disapprove, too conservative—0
Disapprove, too liberal—5
Disapprove, other—0

APPENDIX F

Use of spontaneous breathing trial in weaning ARDS patients

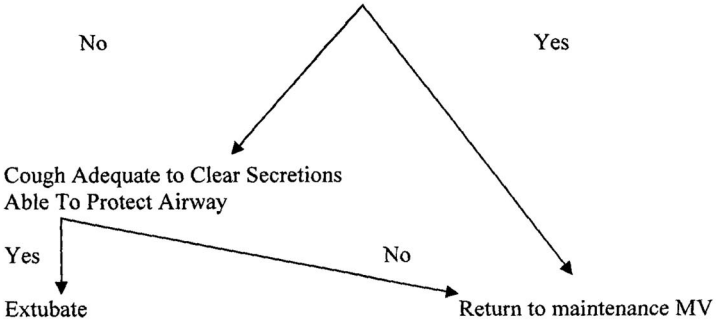
Original illness resolving; no new illness
Off vasopressors and continuous sedatives
Cough during suctioning
$PaO_2/F_IO_2 > 200$
PEEP $\leq$ 5 cm H_2O
Minute ventilation < 15 L min
Frequency/tidal volume (F/TV) ratio $\leq$ 105 during two-minute spontaneous breathing trial

↓

Spontaneous Breathing Trial * (30 to 120 minutes)

Respiratory rate > 35
Oxygen saturation < 90
Pulse > 140/min or change $\geq$ 20%
SBP > 180 mm Hg or < 90 mm Hg
Agitation, diaphoresis, or anxiety
F/TV ratio > 105

Note: Achieving any of these criteria for a sustained period at any time during the trial represents a weaning failure and the need to return to maintenance MV.



PEEP, positive end-expiratory pressure; F/TV, frequency/tidal volume; SBP, systolic blood pressure; MV, mechanical ventilation

*Options include T-Piece, continuous positive airway pressure 5 cm H_2O or low level (5- 10 cm H_2O typically based on ET tube size) pressure support ventilation (167-170)

Appendix H. Selective Digestive Decontamination Nominal Group Vote

Antibiotics	Strong for Use	Weak for Use	Neutral	Weak for Not Using	Strong for Not Using
Systemic and oral	—	9	4	8	1
Systemic alone	—	2	7	5	3

APPENDIX I

2008 SSC Guidelines Committee

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[a]American Association of Critical-Care Nurses; [b]Japanese Association for Acute Medicine; [c]European Society of Intensive Care Medicine; [d]Surgical Infection Society; [e]Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Group; [f]Japanese Society of Intensive Care Medicine; [g]Society of Critical Care Medicine; [h]American College of Emergency Physicians; [i]Canadian Critical Care Society; [j]European Society of Clinical Microbiology and Infectious Diseases; [k]German Sepsis Society; [l]Latin American Sepsis Institute; [m]American College of Chest Physicians; [n]International Sepsis Forum; [o]European Respiratory Society.

APPENDIX J

Author Disclosure Information 2006–2007

Dr. Dellinger has consulted for AstraZeneca, Talecris, and B Braun. He has received honoraria from Eli Lilly (2), Brahms (2), INO Therapeutics (1), Pulsion (1), and bioMerieux (1). He has also received grant support from AstraZeneca and Artisan.

Dr. Levy has received honoraria from Eli Lilly and Edwards Lifesciences. He has also received grant support from Philips Medical Systems, Edwards Lifesciences, Philips Medical Systems, Novartis, Biosite, and Eisai.

Dr. Carlet has consulted for Forrest, Wyeth, Chiron, bioMerieux, and GlaxoSmithKline. He has also received honoraria from Eli Lilly, Becton Dickinson, Jansen, Cook, AstraZeneca, Hutchinson, Bayer, Gilead, MSD, and Targanta.

Dr. Bion has not disclosed any potential conflicts of interest.

Dr. Parker has consulted for Johnson & Johnson.

Dr. Jaeschke has received honoraria from AstraZeneca, Boehringer, Eli Lilly, GlaxoSmithKline, and MSD.

Dr. Reinhart has consulted for Eli Lilly and Edwards Lifesciences. He has also received honoraria from B Braun and royalties from Edwards Lifesciences.

Dr. Angus has consulted for or received speaking fees from AstraZeneca, Brahms Diagnostica, Eisai, Eli Lilly, GlaxoSmithKline, OrthoBiotech, Takeda, and Wyeth-Ayerst. He has also received grant support from GlaxoSmithKline, Ortho-Biotech, and Amgen.

Dr. Brun-Buisson has not disclosed any potential conflicts of interest.

Dr. Beale has received honoraria from Eisai and speaking fees (paid to university) from Lilly UK, Philips, Lidco, and Chiron.

Dr. Calandra has consulted for Baxter, received honoraria from Roche Diagnostics, and received grant support from Baxter and Roche Diagnostics. He also served on the advisory board for Biosite.

Dr. Dhainaut has consulted for Eli Lilly and Novartis. He has also received honoraria from Eli Lilly.

Dr. Gerlach has not disclosed any potential conflicts of interest.

Ms. Harvey has not disclosed any potential conflicts of interest.

Dr. Marini has consulted for KCI and received honoraria from Maquet.

Dr. Marshall has consulted for Becton Dickinson, Takeda, Pfizer, Spectral Diagnostics, Eisai, and Leo-Pharma. He has also received honoraria from Spectral Diagnostics.

Dr. Ranieri has served on the advisory board for Maquet and received support for a sponsored trial from Eli Lilly. He has also received grant support from Tyco, Draeger, and Hamilton.

Dr. Ramsay has consulted for Edwards Lifesciences and Respironics.

Dr. Sevransky has not disclosed any potential conflicts of interest.

Dr. Thompson has consulted for Eli Lilly, Abbott, and AstraZeneca. He has also received grant support from the NIH for a study on computerized glucose control.

Dr. Townsend has not disclosed any potential conflicts of interest.

Dr. Vender has consulted and received honoraria from Eli Lilly.

Dr. Zimmerman has not disclosed any potential conflicts of interest.

Dr. Vincent has consulted for AstraZeneca, Biosite, bioMerieux, Edwards Lifesciences, Eli Lilly, Eisai, Ferring, GlaxoSmithKline, Intercell, Merck, Novartis, NovoNordisk, Organon, Pfizer, Philips Medical Systems, Roche Diagnostics, Spectral Diagnostics, Takeda, and Wyeth-Lederle. He has also received honoraria from Eli Lilly, Edwards Lifesciences, Eisai, GlaxoSmithKline, Novartis, NovoNordisk, and Pfizer.