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

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

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

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

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

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* Members of the 2012 SSC Guidelines Committee and Pediatric Subgroup are listed in **Appendix A** at the end of this article.

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before antibiotic therapy (1C); imaging studies performed promptly to confirm a potential source of infection (UG); administration of broad-spectrum antimicrobials therapy within 1 hr of recognition of septic shock (1B) and severe sepsis without septic shock (1C) as the goal of therapy; reassessment of antimicrobial therapy daily for de-escalation, when appropriate (1B); infection source control with attention to the balance of risks and benefits of the chosen method within 12 hrs of diagnosis (1C); initial fluid resuscitation with crystalloid (1B) and consideration of the addition of albumin in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure (2C) and the avoidance of hetastarch formulations (1C); initial fluid challenge in patients with sepsis-induced tissue hypoperfusion and suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (more rapid administration and greater amounts of fluid may be needed in some patients) (1C); fluid challenge technique continued as long as hemodynamic improvement, as based on either dynamic or static variables (UG); norepinephrine as the first-choice vasopressor to maintain mean arterial pressure ≥ 65 mm Hg (1B); epinephrine when an additional agent is needed to maintain adequate blood pressure (2B); vasopressin (0.03 U/min) can be added to norepinephrine to either raise mean arterial pressure to target or to decrease norepinephrine dose but should not be used as the initial vasopressor (UG); dopamine is not recommended except in highly selected circumstances (2C); dobutamine infusion administered or added to vasopressor in the presence of a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or b) ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure (1C); avoiding use of intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (2C); hemoglobin target of 7–9 g/dL in the absence of tissue hypoperfusion, ischemic coronary artery disease, or acute hemorrhage (1B); low tidal volume (1A) and limitation of inspiratory plateau pressure (1B) for acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure (PEEP) in ARDS (1B); higher rather than lower level of PEEP for patients with sepsis-induced moderate or severe ARDS (2C); recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (2C); prone positioning in sepsis-induced ARDS patients with a Pao_2/Fio_2 ratio of ≤ 100 mm Hg in facilities that have experience with such practices (2C); head-of-bed elevation in mechanically ventilated patients unless contraindicated (1B); a conservative fluid strategy for patients with established ARDS who do not have evidence of tissue hypoperfusion (1C); protocols for weaning and sedation (1A); minimizing use of either intermittent bolus sedation or continuous infusion sedation targeting specific titration endpoints (1B); avoidance of neuromuscular blockers if possible in the septic patient *without* ARDS (1C); a short course of neuromuscular blocker (no longer than 48 hrs) for patients *with* early ARDS and a $Pao_2/Fio_2 < 150$ mm Hg (2C); a protocolized approach to blood glucose management commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL, targeting an upper blood glucose ≤ 180 mg/dL (1A); equivalency of continuous veno-venous hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1B); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding in patients with bleeding risk factors (1B); oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hrs after a diagnosis of severe sepsis/septic shock (2C); and addressing goals of care, including treatment plans and end-of-life planning (as appropriate) (1B), as early as feasible, but within 72 hrs of intensive care unit admission (2C). Recommendations specific to pediatric severe sepsis include: therapy with face mask oxygen, high flow nasal cannula oxygen, or nasopharyngeal continuous PEEP in the presence of respiratory distress and hypoxemia (2C), use of physical examination therapeutic endpoints such as capillary refill (2C); for septic shock associated with hypovolemia, the use of crystalloids or albumin to deliver a bolus of 20 mL/kg of crystalloids (or albumin equivalent) over 5 to 10 mins (2C); more common use of inotropes and vasodilators for low cardiac output septic shock associated with elevated systemic vascular resistance (2C); and use of hydrocortisone only in children with suspected or proven "absolute"' adrenal insufficiency (2C).

Conclusions: Strong agreement existed among a large cohort of international experts regarding many level 1 recommendations for the best care of patients with severe sepsis. Although a significant number of aspects of care have relatively weak support, evidence-based recommendations regarding the acute management of sepsis and septic shock are the foundation of improved outcomes for this important group of critically ill patients. (*Crit Care Med* 2013; 41:580–637)

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

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Sponsoring organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Asia Pacific Association of Critical Care Medicine, Australian and New Zealand Intensive Care Society, Brazilian Society of Critical Care, Canadian Critical Care Society, Chinese Society of Critical Care Medicine, Chinese Society of Critical Care Medicine—China Medical Association, Emirates Intensive Care Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Society of Pediatric and Neonatal Intensive Care, Infectious Diseases Society of America, Indian Society of Critical Care Medicine, International Pan Arabian Critical Care Medicine Society, Japanese Association for Acute Medicine, Japanese Society of Intensive Care Medicine, Pediatric Acute Lung Injury and Sepsis Investigators, Society for Academic Emergency Medicine, Society of Critical Care Medicine, Society of Hospital Medicine, Surgical Infection Society, World Federation of Critical Care Nurses, World Federation of Pediatric Intensive and Critical Care Societies; World Federation of Societies of Intensive and Critical Care Medicine. Participation and endorsement: The German Sepsis Society and the Latin American Sepsis Institute.

Dr. Dellinger consulted for Biotest (immunoglobulin concentrate available in Europe for potential use in sepsis) and AstraZeneca (anti-TNF compound unsuccessful in recently completed sepsis clinical trial); his institution received consulting income from IKARIA for new product development (IKARIA has inhaled nitric oxide available for off-label use in ARDS) and grant support from Spectral Diagnostics Inc (current endotoxin removal clinical trial), Ferring (vasopressin analog clinical trial-ongoing); as well as serving on speakers bureau for Eisai (anti-endotoxin compound that failed to show benefit in clinical trial).

Dr. Levy received grant support from Eisai (Ocean State Clinical Coordinating Center to fund clinical trial [$500K]), he received honoraria from Eli Lilly (lectures in India $8,000), and he has been involved with the Surviving Sepsis Campaign guideline from its beginning.

Dr. Rhodes consulted for Eli Lilly with monetary compensation paid to himself as well as his institution (Steering Committee for the PROWESS Shock trial) and LiDCO; travel/accommodation reimbursement was received from Eli Lilly and LiDCO; he received income for participation in review activities such as data monitoring boards, statistical analysis from Orion, and for Eli Lilly; he is an author on manuscripts describing early goal-directed therapy, and believes in the concept of minimally invasive hemodynamic monitoring.

Dr. Annane participated on the Fresenius Kabi International Advisory Board (honorarium 2000€). His nonfinancial disclosures include being the principal investigator of a completed investigator-led multicenter randomized controlled trial assessing the early guided benefit to risk of NIRS tissue oxygen saturation; he was the principal investigator of an investigator-led randomized controlled trial of epinephrine vs norepinephrine (CATS study)–*Lancet* 2007; he also is the principle investigator of an ongoing investigator-led multinational randomized controlled trial of crystalloids vs colloids (Crystal Study).

Dr. Gerlach has disclosed that he has no potential conflicts of interest; he is an author of a review on the use of activated protein C in surgical patients (published in the *New England Journal of Medicine*, 2009).

Dr. Opal consulted for Genzyme Transgenics (consultant on transgenic antithrombin $1,000), Pfizer (consultant on TLR4 inhibitor project $3,000), British Therapeutics (consultant on polyclonal antibody project $1,000), and Biotest A (consultant on immunoglobul project $2,000). His institution received grant support from Novartis (Clinical Coordinating Center to assist in patient enrollment in a phase III trial with the use of Tissue Factor Pathway Inhibitor [TFPI] in severe community acquired pneumonia [SCAP] $30,000 for 2 years), Eisai ($30,000 for 3 years), Astra Zeneca ($30,000 for 1 year), Aggenix ($30,000 for 1 year), Inimex ($10,000), Eisai ($10,000), Atoxbio ($10,000), Wyeth ($20,000), Sirtris (preclinical research $50,000), and Cellular Bioengineering Inc. ($500). He received honoraria from Novartis (clinical evaluation committee TFPI study for SCAP $20,000) and Eisai ($25,000). He received travel/accommodations reimbursed from Sangart (data and safety monitoring $2,000), Spectral Diagnostics (data and safety monitoring $2,000), Takeda (data and safety monitoring $2,000) and Canadian trials group ROS II oseltamivir study (data and safety monitoring board (no money). He is also on the Data Safety Monitoring Board for Tetraphase (received US $600 in 2012).

Dr. Sevransky received grant support to his institution from Sirius Genomics Inc; he consulted for Idaho Technology ($1,500); he is the co-principal investigator of a multicenter study evaluating the association between intensive care unit organizational and structural factors, including protocols and in-patient mortality. He maintains that protocols serve as useful reminders to busy clinicians to consider certain therapies in patients with sepsis or other life-threatening illness.

Dr. Sprung received grants paid to his institution from Artisan Pharma ($25,000–$50,000), Eisai, Corp ($1,000–$5,000 ACCESS), Ferring Pharmaceuticals A/S ($5,000–$10,000), Hutchinson Technology Incorporated ($1,000–$5,000), Novartis Corp (less than $1,000). His institution receives grant support for patients enrolled in clinical studies from Eisai Corporation (PI. Patients enrolled in the ACCESS study $50,000–$100,000), Takeda (PI. Study terminated before patients enrolled). He received grants paid to his institution and consulting income from Artisan Pharma/Asahi Kasei Pharma America Corp ($25,000–$50,000). He consulted for Eli Lilly (Sabbatical Consulting fee $10,000–$25,000) and received honoraria from Eli Lilly (lecture $1,000–$5,000). He is a member of the Australia and New Zealand Intensive Care Society Clinical Trials Group for the NICE-SUGAR Study (no money received); he is a council member of the International Sepsis Forum (as of Oct. 2010); he has held long time research interests in steroids in sepsis, PI of Corticus study, end-of-life decision making and PI of Ethicus, Ethicatt, and Welpicus studies.

Dr. Douglas received grants paid to his institution from Eli Lilly (PROWESS Shock site), Eisai (study site), National Institutes of Health (ARDS Network), Accelr8 (VAP diagnostics), CCCTG (Oscillate Study), and Hospira (Dexmedetomidine in Alcohol Withdrawal RCT). His institution received an honorarium from the Society of Critical Care Medicine (Paragon ICU Improvement); he consulted for Eli Lilly (PROWESS Shock SC and Sepsis Genomics Study) in accordance with institutional policy; he received payment for providing expert testimony (Smith Moore Leatherwood LLP); travel/accommodations reimbursed by Eli Lilly and Company (PROWESS Shock Steering Committee) and the Society of Critical Care Medicine (Hospital Quality Alliance, Washington DC, four times per year 2009—2011); he received honoraria from Covidien (non-CME lecture 2010, US$500) and the University of Minnesota Center for Excellence in Critical Care CME program (2009, 2010); he has a pending patent for a bed backrest elevation monitor.

Dr. Jaeschke has disclosed that he has no potential conflicts of interest.

Dr. Osborn consulted for Sui Generis Health ($200). Her institution receives grant support from the National Institutes of Health Research, Health Technology Assessment Programme-United Kingdom (trial doctor for sepsis-related RCT). Salary paid through the NIHR government funded (nonindustry) grant. Grant awarded to chief investigator from ICNARC. She is a trial clinician for ProMISe.

Dr. Nunnally received a stipend for a chapter on diabetes mellitus; he is an author of editorials contesting classic tight glucose control.

Dr. Townsend is an advocate for healthcare quality improvement.

Dr. Reinhart consulted for EISAI (Steering Committee member—less then US $10,000); BRAHMS Diagnostics (less than US $10,000); and SIRS-Lab Jena (founding member, less than US $10,000). He received honoraria for lectures including service on the speakers' bureau from Biosyn Germany (less than €10,000) and Braun Melsungen (less than €10,000). He received royalties from Edwards Life Sciences for sales of central venous oxygen catheters (~$100,000).

Dr. Kleinpell received monetary compensation for providing expert testimony (four depositions and one trial in the past year). Her institution receives grants from the Agency for Healthcare Research and Quality and the Prince Foundation (4-year R01 grant, PI and 3-year foundation grant, Co-I). She received honoraria from the Cleveland Clinic and the American Association of Critical Care Nurses for keynote speeches at conferences; she received royalties from McGraw Hill (co-editor of critical care review book); travel/accommodations reimbursed from the American Academy of Nurse Practitioners, Society of Critical Care Medicine, and American Association of Critical Care Nurses (one night hotel coverage at national conference).

Dr. Angus consulted for Eli Lilly (member of the Data Safety Monitoring Board, Multicenter trial of a PC for septic shock), Eisai Inc (Anti-TLR4 therapy for severe sepsis), and Idaho Technology (sepsis biomarkers); he received grant support (investigator, long-term follow-up of phase III trial of an anti-TLR4 agent in severe sepsis), a consulting income (anti-TRL4 therapy for severe sepsis), and travel/accommodation expense reimbursement from Eisai, Inc; he is the primary investigator for an ongoing National Institutes of Health-funded study comparing early resuscitation strategies for sepsis-induced tissue hypoperfusion.

Dr. Deutschman has nonfinancial involvement as a coauthor of the Society of Critical Care Medicine's Glycemic Control guidelines.

Dr. Machado reports unrestricted grant support paid to her institution for Surviving Sepsis Campaign implementation in Brazil (Eli Lilly do Brasil); she is the primary investigator for an ongoing study involving vasopressin.

Dr. Rubenfeld received grant support from nonprofit agencies or foundations including National Institutes of Health ($10 million), Robert Wood Johnson Foundation ($500,000), and CIHR ($200,000). His institution received grants from for-profit companies including Advanced Lifeline System ($150,000), Siemens ($50,000), Bayer ($10,000), Byk Gulden ($15,000), AstraZeneca ($10,000), Faron Pharmaceuticals ($5,000), and Cerus Corporation ($11,000). He received honoraria, consulting fees, editorship, royalties, and Data and Safety Monitoring Board membership fees paid to him from Bayer ($500), DHD ($1,000), Eli Lilly ($5,000), Oxford University Press ($10,000), Hospira ($15,000), Cerner ($5,000), Pfizer ($1,000), KCI ($7,500), American Association for Respiratory Care ($10,000), American Thoracic Society ($7,500), BioMed Central ($1,000), National Institutes of Health ($1,500), and the Alberta Heritage Foundation for Medical Research ($250). He has database access or other intellectual (non financial) support from Cerner.

Dr. Webb consulted for AstraZeneca (anti-infectives $1,000—$5,000) and Jansen-Cilag (anti-infectives $1,000-$5,000). He received grant support

from a NHMRC project grant (ARISE RECT of EGDT); NHMRC project grant and Fresinius-unrestricted grant (CHEST RCT of voluven vs. saline); RCT of steroid vs. placebo for septic shock); NHMRC project grant (BLISS study of bacteria detection by PRC in septic shock) Intensive Care Foundation-ANZ (BLING pilot RCT of beta-lactam administration by infusion); Hospira (SPICE programme of sedation delirium research); NHMRC Centres for Research Excellent Grant (critical illness microbiology observational studies); Hospira-unrestricted grant (DAHlia RCT of dexmedetomidine for agitated delirium). Travel/accommodations reimbursed by Jansen-Cilag ($5,000–$10,000) and AstraZeneca ($1,000-$5,000); he has a patent for a meningococcal vaccine. He is chair of the ANZICS Clinical Trials Group and is an investigator in trials of EGDT, PCR for determining bacterial load and a steroid in the septic shock trial.

Dr. Beale received compensation for his participation as board member for Eisai, Inc, Applied Physiology, bioMérieux, Covidien, SIRS-Lab, and Novartis; consulting income was paid to his institution from PriceSpective Ltd, Easton Associates (soluble guanylate cyclase activator in acute respiratory distress syndrome/acute lung injury adjunct therapy to supportive care and ventilation strategies), Eisai (eritoran), and Phillips (Respironics); he provided expert testimony for Eli Lilly and Company (paid to his institution); honoraria received (paid to his institution) from Applied Physiology (Applied Physiology PL SAB, Applied Physiology SAB, Brussels, Satellite Symposium at the ISICEM, Brussels), bioMérieux (GeneXpert Focus Group, France), SIRS-Lab (SIRS-LAB SAB Forum, Brussels and SIRS-LAB SAB, Lisbon), Eli Lilly (CHMP Hearing), Eisai (eritoran through leader touch plan in Brussels), Eli Lilly (Lunchtime Symposium, Vienna), Covidien (adult monitoring advisory board meeting, Frankfurt), Covidien (Global Advisory Board CNIBP Boulder USA), Eli Lilly and Company (development of educational presentations including service on speaker' bureaus (intensive care school hosted in department); travel/accommodations were reimbursed from bioMerieux (GeneXpert Focus Group, France) and LiDCO (Winter Anaesthetic and Critical Care Review Conference), Surviving Sepsis Campaign (Publications Meeting, New York; Care Bundles Conference, Manchester), SSC Publication Committee Meeting and SSC Executive Committee Meeting, Nashville; SSC Meeting, Manchester), Novartis (Advisory Board Meeting, Zurich), Institute of Biomedical Engineering (Hospital of the Future Grand Challenge Kick-Off Meeting, Hospital of the Future Grand Challenge Interviews EPSRC Headquarters, Swindon, Philips (Kick-Off Meeting, Boeblingen, Germany; MET Conference, Cohenhagen), Covidien (Adult Monitoring Advisory Board Meeting, Frankfurt), Eisai (ACCESS Investigators Meeting, Barcelona). His nonfinancial disclosures include authorship of the position statement on fluid resuscitation from the ESICM task force on colloids (yet to be finalized).

Dr. Vincent reports consulting income paid to his institution from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, GlaxoSmithKline, Merck, and Pfizer. His institution received honoraria on his behalf from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, Merck, and Pfizer. His institution received grant support from Astellas, Curacyte, Eli Lilly, Eisai, Ferring, and Pfizer. His institution received payment for educational presentations from Astellas, AstraZeneca, Curacyte, Eli Lilly, Eisai, Ferring, Merck, and Pfizer.

Dr. Moreno consulted for bioMerieux (expert meeting). He is a coauthor of a paper on corticosteroids in patients with septic shock. He is the author of several manuscripts defining sepsis and stratification of the patient with sepsis. He is also the author of several manuscripts contesting the utility of sepsis bundles.

Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). Severe sepsis and septic shock are major healthcare problems, affecting millions of people 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.

The recommendations in this document 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 presented with a patient's unique set of clinical variables. Most of these recommendations are appropriate for the severe sepsis patient in the ICU and non-ICU settings. In fact, the committee believes that 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. Resource limitations in some institutions and countries may prevent physicians from accomplishing particular recommendations. Thus, these recommendations are intended to be best practice (the committee considers this a goal for clinical practice) and not created to represent standard of care. The Surviving Sepsis Campaign (SSC) Guidelines Committee hopes that over time, particularly through education programs and formal audit and feedback performance improvement initiatives, the guidelines will influence bedside healthcare practitioner behavior that will reduce the burden of sepsis worldwide.

METHODOLOGY

Definitions

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (**Tables 1** and **2**) (6). Throughout this manuscript and the performance improvement bundles, which are included, a distinction is made between definitions and therapeutic targets or thresholds. Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension. An example of a therapeutic target or typical threshold for the reversal of hypotension is seen in the sepsis bundles for the use of vasopressors. In the bundles, the MAP *threshold* is ≥ 65 mm Hg. The use of *definition vs. threshold* will be evident throughout this article. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.

History of the Guidelines

These clinical practice guidelines are a revision of the 2008 SSC guidelines for the management of severe sepsis and septic shock (7). The initial SSC guidelines were published in 2004 (8) and incorporated the evidence available through the end of 2003. The 2008 publication analyzed evidence available through the end of 2007. The most current iteration is based on updated literature search incorporated into the evolving manuscript through fall 2012.

Selection and Organization of Committee Members

The selection of committee members was based on interest and expertise in specific aspects of sepsis. Co-chairs and executive committee members were appointed by the Society of Critical Care Medicine and European Society of Intensive Care Medicine governing bodies. Each sponsoring organization appointed a representative who had sepsis expertise. Additional committee members were appointed by the co-chairs and executive committee to create continuity with the previous committees' membership as well as to address content needs for the development process. Four clinicians with experience in the GRADE process application (referred to in this document as GRADE group or Evidence-Based Medicine [EBM] group) took part in the guidelines development.

The guidelines development process began with appointment of group heads and assignment of committee members to groups according to their specific expertise. Each group was responsible for drafting the initial update to the 2008 edition in their assigned area (with major additional elements of information incorporated into the evolving manuscript through year-end 2011 and early 2012).

With input from the EBM group, an initial group meeting was held to establish procedures for literature review and development of tables for evidence analysis. Committees and their subgroups continued work via phone and the Internet. Several subsequent meetings of subgroups and key individuals occurred at major international meetings (nominal groups), with work continuing via teleconferences and electronic-based discussions among subgroups and members of the entire committee. Ultimately, a meeting of all group heads, executive committee members, and other key committee members was held to finalize the draft document for submission to reviewers.

Search Techniques

A separate literature search was performed for each clearly defined question. The committee chairs worked with subgroup heads to identify pertinent search terms that were to include, at a minimum, *sepsis, severe sepsis, septic shock,* and *sepsis syndrome* crossed against the subgroup's general topic area, as well as appropriate key words of the specific question posed. All questions used in the previous guidelines publications were searched, as were pertinent new questions generated by general topic-related searches or recent trials. The authors were specifically asked to look for existing meta-analyses related to their question and search a minimum of one general database (ie, MEDLINE, EMBASE) and the Cochrane Library (both The Cochrane Database of Systematic Reviews [CDSR] and Database of Abstracts of Reviews of Effectiveness [DARE]). Other databases were optional (ACP Journal Club, *Evidence-Based Medicine Journal*, Cochrane Registry of Controlled Clinical Trials, International Standard Randomized Controlled Trial Registry [http://www.controlled-trials.com/isrctn/] or *meta*Register of Controlled Trials [http://www.controlled-trials.com/mrct/]. Where appropriate, available evidence was summarized in the form of evidence tables.

Grading of Recommendations

We advised the authors to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations (**Tables 3** and **4**). (9–11). The SSC Steering Committee and individual authors collaborated with GRADE representatives to apply the system during the SSC guidelines revision process. The members of the 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.

The GRADE system is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between the benefits and risks, burden, and cost, leading to development and grading of a management recommendation. 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), moderate (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 3). Examples of indirectness of the evidence include population studied, interventions used, outcomes measured, and how these relate to the question of interest. Well-done observational (nonrandomized) studies begin as low-quality evidence, but the quality level may be upgraded on the basis of a large magnitude of effect. An example of this is the quality of evidence for early administration of antibiotics. References to supplemental digital content appendices of GRADEpro Summary of Evidence Tables appear throughout this document.

The GRADE system classifies recommendations as strong (grade 1) or weak (grade 2). The factors influencing this determination are presented in Table 4. The assignment 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 would outweigh the undesirable effects, and the strength of a recommendation reflects the group's degree of confidence in that assessment. Thus, a strong recommendation in favor of an intervention reflects the panel's opinion that the desirable effects of adherence to a recommendation (beneficial health outcomes; lesser burden on staff and patients; and cost savings) will clearly outweigh the undesirable effects (harm to health; more burden on staff and patients; and greater costs). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were taken into account. A weak recommendation in favor of an intervention indicates the judgment 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 uncertainty remains regarding the benefits and risks) or the

TABLE 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 more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
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 greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two 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 less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr 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 aPTT > 60 s)
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 (> 1 mmol/L)
Decreased capillary refill or mottling

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

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° 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.

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.

benefits and downsides are closely balanced. A strong recommendation is worded as "we recommend" and a weak recommendation as "we suggest."

Throughout the document are a number of statements that either follow graded recommendations or are listed as stand-alone numbered statements followed by "ungraded" in parentheses (UG). In the opinion of the committee, these recommendations were not conducive for the GRADE process.

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. Circumstances may exist in which a strong recommendation cannot or should not be followed for an individual because of that patient's preferences or clinical characteristics that make the recommendation less applicable. A strong recommendation does not automatically imply standard of care. For example, the strong recommendation

TABLE 2. Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury 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 μL
Coagulopathy (international normalized ratio > 1.5)

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.

for administering antibiotics within 1 hr of the diagnosis of severe sepsis, as well as the recommendation for achieving a central venous pressure (CVP) of 8 mm Hg and a central venous oxygen saturation ($Scvo_2$) of 70% in the first 6 hrs of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet standards of care as verified by practice data.

Significant education of committee members on the GRADE approach built on the process conducted during 2008 efforts. Several members of the committee were trained in the use of GRADEpro software, allowing more formal use of the GRADE system (12). Rules were distributed concerning assessing the body of evidence, and GRADE representatives were available for advice throughout the process. Subgroups agreed electronically on draft proposals that were then presented for general discussion among subgroup heads, the SSC Steering Committee (two co-chairs, two co-vice chairs, and an at-large committee member), and several selected key committee members who met in July 2011 in Chicago. The results of that discussion were incorporated into the next version of recommendations and again discussed with the whole group using electronic mail. Draft recommendations were distributed to the entire committee and finalized during an additional nominal group meeting in Berlin in October 2011. Deliberations and decisions were then recirculated to the entire committee for approval. At the discretion of the chairs

TABLE 3. Determination of the Quality of Evidence

Underlying methodology
A (high) RCTs
B (moderate) Downgraded RCTs or upgraded observational studies
C (low) Well-done observational studies with control RCTs
D (very low) Downgraded controlled studies or expert opinion based on other evidence
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, relative risk > 2 with no plausible confounders)
2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels)
3. Dose-response gradient

RCT = randomized controlled trial.

TABLE 4. Factors Determining Strong vs. Weak Recommendation

What Should be Considered	Recommended Process
High or moderate evidence (*Is there high or moderate quality evidence?*)	The higher the quality of evidence, the more likely a strong recommendation.
Certainty about the balance of benefits vs. harms and burdens (*Is there certainty?*)	The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.
Certainty in or similar values (*Is there certainty or similarity?*)	The more certainty or similarity in values and preferences, the more likely a strong recommendation.
Resource implications (*Are resources worth expected benefits?*)	The lower the cost of an intervention compared to the alternative and other costs related to the decision–ie, fewer resources consumed–the more likely a strong recommendation.

and following discussion, competing proposals for wording of recommendations or assigning strength of evidence were resolved by formal voting within subgroups and at nominal group meetings. The manuscript was edited for style and form by the writing committee with final approval by subgroup heads and then by the entire committee. To satisfy peer review during the final stages of manuscript approval for publication, several recommendations were edited with approval of the SSC executive committee group head for that recommendation and the EBM lead.

Conflict of Interest Policy

Since the inception of the SSC guidelines in 2004, no members of the committee represented industry; there was no industry input into guidelines development; and no industry representatives were present at any of the meetings. Industry awareness or comment on the recommendations was not allowed. No member of the guidelines committee received honoraria for any role in the 2004, 2008, or 2012 guidelines process.

A detailed description of the disclosure process and all author disclosures appear in Supplemental Digital Content 1 (http://links.lww.com/CCM/A615) in the supplemental materials to this document. **Appendix B** shows a flowchart of the COI disclosure process. Committee members who were judged to have either financial or nonfinancial/academic competing interests were recused during the closed discussion session and voting session on that topic. Full disclosure and transparency of all committee members' potential conflicts were sought.

On initial review, 68 financial conflict of interest (COI) disclosures and 54 nonfinancial disclosures were submitted by committee members. Declared COI disclosures from 19 members were determined by the COI subcommittee to be not relevant to the guidelines content process. Nine who were determined to have COI (financial and nonfinancial) were adjudicated by group reassignment and requirement to adhere to SSC COI policy regarding discussion or voting at any committee meetings where content germane to their COI was discussed. Nine were judged as having conflicts that could not be resolved solely by reassignment. One of these individuals was asked to step down from the committee. The other eight were assigned to the groups in which they had the least COI. They were required to work within their group with full disclosure when a topic for which they had relevant COI was discussed, and they were not allowed to serve as group head. At the time of final approval of the document, an update of the COI statement was required. No additional COI issues were reported that required further adjudication.

MANAGEMENT OF SEVERE SEPSIS

Initial Resuscitation and Infection Issues (Table 5)

A. Initial Resuscitation

1. We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 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 a part of a treatment protocol (grade 1C):
   a) CVP 8–12 mm Hg
   b) MAP ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL·kg·hr
   d) Superior vena cava oxygenation saturation (Scv_{O_2}) or mixed venous oxygen saturation (Sv_{O_2}) 70% or 65%, respectively.
2. We suggest targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (grade 2C).

Rationale. In a randomized, controlled, single-center study, early quantitative resuscitation improved survival for emergency department patients presenting with septic shock (13). Resuscitation targeting the physiologic goals expressed in recommendation 1 (above) for the initial 6-hr period was associated with a 15.9% absolute reduction in 28-day mortality rate. This strategy, termed *early goal-directed therapy*, was evaluated in a multicenter trial of 314 patients with severe sepsis in eight Chinese centers (14). This trial reported a 17.7% absolute reduction in 28-day mortality (survival rates, 75.2% vs. 57.5%,

$p = 0.001$). A large number of other observational studies using similar forms of early quantitative resuscitation in comparable patient populations have shown significant mortality reduction compared to the institutions' historical controls (**Supplemental Digital Content 2,** http://links.lww.com/CCM/A615). Phase III of the SSC activities, the international performance improvement program, showed that the mortality of septic patients presenting with both hypotension and lactate ≥ 4 mmol/L was 46.1%, similar to the 46.6% mortality found in the first trial cited above (15). As part of performance improvement programs, some hospitals have lowered the lactate threshold for triggering quantitative resuscitation in the patient with severe sepsis, but these thresholds have not been subjected to randomized trials.

The consensus panel judged use of CVP and Svo_2 targets to be recommended physiologic targets for resuscitation. Although there are limitations to CVP as a marker of intravascular volume status and response to fluids, a low CVP generally can be relied upon as supporting positive response to fluid loading. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. During the first 6 hrs of resuscitation, if $Scvo_2$ less than 70% or Svo_2 equivalent of less than 65% persists with what is judged to be adequate intravascular volume repletion in the presence of persisting tissue hypoperfusion, then dobutamine infusion (to a maximum of 20 μg/kg/min) or transfusion of packed red blood cells to achieve a hematocrit of greater than or equal to 30% in attempts to achieve the $Scvo_2$ or Svo_2 goal are options. The strong recommendation for achieving a CVP of 8 mm Hg and an $Scvo_2$ of 70% in the first 6 hrs of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet the standard of care as verified by practice data. The publication of the initial results of the international SSC performance improvement program demonstrated that adherence to CVP and $Scvo_2$ targets for initial resuscitation was low (15).

TABLE 5. Recommendations: Initial Resuscitation and Infection Issues

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

B. Screening for Sepsis and Performance Improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital–based performance improvement efforts in severe sepsis (UG).

C. Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).
2. Use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

D. Antimicrobial Therapy

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

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

(*Continued*)

TABLE 5. (*Continued*) Recommendations: Initial Resuscitation and Infection Issues

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

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

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

F. Infection Prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

In mechanically ventilated patients or those with known preexisting decreased ventricular compliance, a higher target CVP of 12 to 15 mm Hg should be achieved to account for the impediment in filling (16). Similar consideration may be warranted in circumstances of increased abdominal pressure (17). Elevated CVP may also be seen with preexisting clinically significant pulmonary artery hypertension, making use of this variable untenable for judging intravascular volume status. 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. Published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥ 65 mm Hg as well as Scv_{O_2} ≥ 70% (measured in the superior vena cava, either intermittently or continuously [18]). Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion (19–24). Studies of patients with shock indicate that Sv_{O_2} runs 5% to 7% lower than Scv_{O_2} (25). While the committee recognized the controversy surrounding resuscitation targets, an early quantitative resuscitation protocol using CVP and venous blood gases can be readily established in both emergency department and ICU settings (26). Recognized limitations to static ventricular filling pressure estimates exist as surrogates for fluid resuscitation (27, 28), but measurement of CVP is currently the most readily obtainable target for fluid resuscitation. Targeting dynamic measures of fluid responsiveness during resuscitation, including flow and possibly volumetric indices and microcirculatory changes, may have advantages (29–32). Available technologies allow measurement of flow at the bedside (33, 34); however, the efficacy of these monitoring techniques to influence clinical outcomes from early sepsis resuscitation remains incomplete and requires further study before endorsement.

The global prevalence of severe sepsis patients initially presenting with either hypotension with lactate ≥ 4 mmol//L, hypotension alone, or lactate ≥ 4 mmol/L alone, is reported as 16.6%, 49.5%, and 5.4%, respectively (15). The mortality rate is high in septic patients with both hypotension and lactate ≥ 4 mmol/L (46.1%) (15), and is also increased in severely septic patients with hypotension alone (36.7%) and lactate ≥ 4 mmol/L alone (30%) (15). If Scv_{O_2} is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. Scv_{O_2} and lactate normalization may also be used as a combined endpoint when both are available. Two multicenter randomized trials evaluated a resuscitation strategy that included lactate reduction as a single target or a target combined with Scv_{O_2} normalization (35, 36). The first trial reported that early quantitative resuscitation based on lactate clearance (decrease by at least 10%) was noninferior to early quantitative resuscitation based on achieving Scv_{O_2} of 70% or more (35). The intention-to-treat group contained 300, but the number of patients actually requiring either Scv_{O_2} normalization or lactate clearance was small ($n = 30$). The second trial included

348 patients with lactate levels ≥ 3 mmol/L (36). The strategy in this trial was based on a greater than or equal to 20% decrease in lactate levels per 2 hrs of the first 8 hrs in addition to Scv_{O_2} target achievement, and was associated with a 9.6% absolute reduction in mortality ($p = 0.067$; adjusted hazard ratio, 0.61; 95% CI, 0.43–0.87; $p = 0.006$).

B. Screening for Sepsis and Performance Improvement

1. We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (grade 1C).

Rationale. The early identification of sepsis and implementation of early evidence-based therapies have been documented to improve outcomes and decrease sepsis-related mortality (15). Reducing the time to diagnosis of severe sepsis is thought to be a critical component of reducing mortality from sepsis-related multiple organ dysfunction (35). Lack of early recognition is a major obstacle to sepsis bundle initiation. Sepsis screening tools have been developed to monitor ICU patients (37–41), and their implementation has been associated with decreased sepsis-related mortality (15).

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

Rationale. Performance improvement efforts in sepsis have been associated with improved patient outcomes (19, 42–46). Improvement in care through increasing compliance with sepsis quality indicators is the goal of a severe sepsis performance improvement program (47). Sepsis management requires a multidisciplinary team (physicians, nurses, pharmacy, respiratory, dieticians, and administration) and multispecialty collaboration (medicine, surgery, and emergency medicine) to maximize the chance for success. Evaluation of process change requires consistent education, protocol development and implementation, data collection, measurement of indicators, and feedback to facilitate the continuous performance improvement. Ongoing educational sessions provide feedback on indicator compliance and can help identify areas for additional improvement efforts. In addition to traditional continuing medical education efforts to introduce guidelines into clinical practice, knowledge translation efforts have recently been introduced as a means to promote the use of high-quality evidence in changing behavior (48). Protocol implementation associated with education and performance feedback has been shown to change clinician behavior and is associated with improved outcomes and cost-effectiveness in severe sepsis (19, 23, 24, 49). In partnership with the Institute for Healthcare Improvement, phase III of the Surviving Sepsis Campaign targeted the implementation of a core set ("bundle") of recommendations in hospital environments where change in behavior and clinical impact were measured (50). The SSC guidelines and bundles can be used as the basis of a sepsis performance improvement program.

Application of the SSC sepsis bundles led to sustained, continuous quality improvement in sepsis care and was associated with reduced mortality (15). Analysis of the data from nearly 32,000 patient charts gathered from 239 hospitals in 17 countries through September 2011 as part of phase III of the campaign informed the revision of the bundles in conjunction with the 2012 guidelines. As a result, for the 2012 version, the management bundle was dropped and the resuscitation bundle was broken into two parts and modified as shown in **Figure 1**. For performance improvement quality indicators, resuscitation target thresholds are not considered. However, recommended targets from the guidelines are included with the bundles for reference purposes.

C. Diagnosis

1. We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (> 45 minutes) in the start of antimicrobial(s) administration (grade 1C). To optimize identification of causative organisms, we recommend obtaining at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (< 48 hours) inserted. These blood cultures can be drawn at the same time if they are obtained from different sites. 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 antimicrobial therapy if doing so does not cause significant delay in antibiotic administration (grade 1C).

Rationale. Although sampling should not delay timely administration of antimicrobial agents in patients with severe sepsis (eg, lumbar puncture in suspected meningitis), obtaining appropriate cultures before administration of antimicrobials is essential to confirm infection and the responsible pathogens, and to allow de-escalation of antimicrobial therapy after receipt of the susceptibility profile. Samples can be refrigerated or frozen if processing cannot be performed immediately. Because rapid sterilization of blood cultures can occur within a few hours after the first antimicrobial dose, obtaining those cultures before therapy is essential if the causative organism is to be identified. Two or more blood cultures are recommended (51). In patients with indwelling catheters (for more than 48 hrs), at least one blood culture should be drawn through each lumen of each vascular access device (if feasible, especially for vascular devices with signs of inflammation, catheter dysfunction, or indicators of thrombus formation). 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 equivalent volumes of blood drawn for culture and the vascular access device is positive much earlier than the peripheral blood culture (ie, more than 2 hrs earlier), the data support the concept that the vascular access device is the source of the infection (36, 51, 52). Quantitative cultures of catheter and peripheral blood may also be useful for determining whether the catheter is the source of infection. The volume of blood drawn with the culture tube should be ≥ 10 mL (53).

SURVIVING SEPSIS CAMPAIGN BUNDLES

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

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.

Quantitative (or semiquantitative) cultures of respiratory tract secretions are often recommended for the diagnosis of ventilator-associated pneumonia (54), but their diagnostic value remains unclear (55).

The Gram stain can be useful, in particular for respiratory tract specimens, to determine if inflammatory cells are present (greater than five polymorphonuclear leukocytes/high-powered field and less than ten squamous cells/low-powered field) and if culture results will be informative of lower respiratory pathogens. Rapid influenza antigen testing during periods of increased influenza activity in the community is also recommended. A focused history can provide vital information about potential risk factors for infection and likely pathogens at specific tissue sites. The potential role of biomarkers for diagnosis of infection in patients presenting with severe sepsis remains undefined. The utility of procalcitonin levels or other biomarkers (such as C-reactive protein) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (eg, postoperative, other forms of shock) has not been demonstrated. No recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states (56–58).

In the near future, rapid, non-culture-based diagnostic methods (polymerase chain reaction, mass spectroscopy, microarrays) might be helpful for a quicker identification of pathogens and major antimicrobial resistance determinants (59). These methodologies could be particularly useful for difficult-to-culture pathogens or in clinical situations where empiric antimicrobial agents have been administered before culture samples were been obtained. Clinical experience remains limited, and more clinical studies are needed before recommending these non-culture molecular methods as a replacement for standard blood culture methods (60, 61).

2. We suggest the use of the 1,3 β-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (grade 2C) when invasive candidiasis is in the differential diagnosis of infection.

Rationale. The diagnosis of systemic fungal infection (usually candidiasis) in the critically ill patient can be challenging, and rapid diagnostic methodologies, such as antigen and antibody detection assays, can be helpful in detecting candidiasis in the ICU patient. These suggested tests have shown positive results significantly earlier than standard culture methods (62–67), but false-positive reactions can occur with colonization alone, and their diagnostic utility in managing fungal infection in the ICU needs additional study (65).

3. We recommend that imaging studies be performed promptly in attempts to confirm a potential source of infection. Potential sources of infection should be sampled as they are identified and in consideration of patient risk for transport and invasive procedures (eg, careful coordination and aggressive monitoring if the decision is made to transport for a CT-guided needle aspiration). Bedside studies, such as ultrasound, may avoid patient transport (UG).

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. Even in the most organized and well-staffed healthcare facilities, however, transport of patients can be dangerous, as can be placing patients in outside-unit imaging devices that are difficult to access and monitor. Balancing risk and benefit is therefore mandatory in those settings.

D. Antimicrobial Therapy

1. The administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) should be the goal of therapy. ***Remark:*** Although the weight of the evidence supports prompt administration of antibiotics following the recognition of severe sepsis and septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically evaluated.

Rationale. Establishing vascular access and initiating aggressive fluid resuscitation are the first priorities when managing patients with severe sepsis or septic shock. Prompt infusion of antimicrobial agents should also be a priority and may require additional vascular access ports (68, 69). In the presence of septic shock, each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality in a number of studies (15, 68, 70–72). Overall, the preponderance of data support giving antibiotics as soon as possible in patients with severe sepsis with or without septic shock (15, 68, 70–77). The administration of

antimicrobial agents with a spectrum of activity likely to treat the responsible pathogen(s) effectively within 1 hr of the diagnosis of severe sepsis and septic shock. Practical considerations, for example challenges with clinicians' early identification of patients or operational complexities in the drug delivery chain, represent unstudied variables that may impact achieving this goal. Future trials should endeavor to provide an evidence base in this regard. This should be the target goal when managing patients with septic shock, whether they are located within the hospital ward, the emergency department, or the ICU. The strong recommendation for administering antibiotics within 1 hr of the diagnosis of severe sepsis and septic shock, although judged to be desirable, is not yet the standard of care as verified by published practice data (15).

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. Many antibiotics will not remain stable if premixed in a solution. This risk must be taken into consideration in institutions that rely on premixed solutions for rapid availability of antibiotics. 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 empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

Rationale. The choice of empirical antimicrobial therapy depends on complex issues related to the patient's history, including drug intolerances, recent receipt of antibiotics (previous 3 months), underlying disease, the clinical syndrome, and susceptibility patterns of pathogens in the community and hospital, and that previously have been documented to colonize or infect the patient. The most common pathogens that cause septic shock in hospitalized patients are Gram-positive bacteria, followed by Gram-negative and mixed bacterial microorganisms. Candidiasis, toxic shock syndromes, and an array of uncommon pathogens should be considered in selected patients. An especially wide range of potential pathogens exists for neutropenic patients. Recently used anti-infective agents should generally be avoided. When choosing empirical therapy, clinicians should be cognizant of the virulence and growing prevalence of oxacillin (methicillin)-resistant *Staphylococcus aureus*, and resistance to broad-spectrum beta-lactams and carbapenem among Gram-negative bacilli in some communities and healthcare settings. Within regions in which the prevalence of such drug-resistant organisms is significant, empiric therapy adequate to cover these pathogens is warranted.

Clinicians should also consider whether candidemia is a likely pathogen when choosing initial therapy. When deemed warranted, the selection of empirical antifungal therapy (eg, an echinocandin, triazoles such as fluconazole, or a formulation of amphotericin B) should be tailored to the local pattern of the most prevalent *Candida* species and any recent exposure to antifungal drugs (78). Recent Infectious Diseases Society of America (IDSA) guidelines recommend either fluconazole or an echinocandin. Empiric use of an echinocandin is preferred in most patients with severe illness, especially in those patients who have recently been treated with antifungal agents, or if *Candida glabrata* infection is suspected from earlier culture data. Knowledge of local resistance patterns to antifungal agents should guide drug selection until fungal susceptibility test results, if available, are performed. Risk factors for candidemia, such as immunosuppressed or neutropenic state, prior intense antibiotic therapy, or colonization in multiple sites, 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. Antibiotic choices should be guided by local prevalence patterns of bacterial pathogens and susceptibility data. Ample evidence exists that failure to initiate appropriate therapy (ie, therapy with activity against the pathogen that is subsequently identified as the causative agent) correlates with increased morbidity and mortality in patients with severe sepsis or septic shock (68, 71, 79, 80). Recent exposure to antimicrobials (within last 3 months) should be considered in the choice of an empiric antibacterial regimen. Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antimicrobial susceptibilities are defined. Although a global restriction of antibiotics is an important strategy to reduce the development of antimicrobial resistance and to reduce cost, it is not an appropriate strategy in the initial therapy for this patient population. However, as soon as the causative pathogen has been identified, de-escalation should be performed by selecting the most appropriate antimicrobial agent that covers the pathogen and is safe and cost-effective. Collaboration with antimicrobial stewardship programs, where they exist, is encouraged to ensure appropriate choices and rapid availability of effective antimicrobials for treating septic patients. All patients should receive a full loading dose of each agent. Patients with sepsis often have abnormal and vacillating renal or hepatic function, or may have abnormally high volumes of distribution due to aggressive fluid resuscitation, requiring dose adjustment. Drug serum concentration monitoring can be useful in an ICU setting for those drugs that can be measured promptly. Significant expertise is required to ensure that serum concentrations maximize efficacy and minimize toxicity (81, 82).

2b. The antimicrobial regimen should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1B).

Rationale. Once the causative pathogen has been identified, the most appropriate antimicrobial agent that covers the pathogen and is safe and cost-effective should be selected. On occasion, continued use of specific combinations of antimicrobials might be indicated even after susceptibility testing is available

(eg, *Pseudomonas* spp. only susceptible to aminoglycosides; enterococcal endocarditis; *Acinetobacter* spp. infections susceptible only to polymyxins). Decisions on definitive antibiotic choices should be based on the type of pathogen, patient characteristics, and favored hospital treatment regimens.

Narrowing the spectrum of antimicrobial coverage and reducing the duration of antimicrobial therapy will reduce the likelihood that the patient will develop superinfection with other 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 giving an adequate course of therapy to cure the infection that caused the severe sepsis or septic shock.

3. We suggest the use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection (grade 2C).

Rationale. This suggestion is predicated on the preponderance of the published literature relating to the use of procalcitonin as a tool to discontinue unnecessary antimicrobials (58, 83). However, clinical experience with this strategy is limited and the potential for harm remains a concern (83). No evidence demonstrates that this practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic-related diarrhea from *C. difficile*. One recent study failed to show any benefit of daily procalcitonin measurement in early antibiotic therapy or survival (84).

4a. Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon each patient's presenting illness and local patterns of infection. We suggest combination empiric therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For selected patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is suggested for *P. aeruginosa* bacteremia (grade 2B). Similarly, a more complex combination of beta-lactam and a macrolide is suggested for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

Rationale. Complex combinations might be needed in settings where highly antibiotic-resistant pathogens are prevalent, with such regimens incorporating carbapenems, colistin, rifampin, or other agents. However, a recent controlled trial suggested that adding a fluoroquinolone to a carbapenem as empiric therapy did not improve outcome in a population at low risk for infection with resistant microorganisms (85).

4b. We suggest that combination therapy, when used empirically in patients with severe sepsis, should not be administered for longer than 3 to 5 days. De-escalation to the most appropriate single-agent therapy should be performed as soon as the susceptibility profile is known (grade 2B). Exceptions would include aminoglycoside monotherapy, which should be generally avoided, particularly for *P. aeruginosa* sepsis, and for selected forms of endocarditis, where prolonged courses of combinations of antibiotics are warranted.

Rationale. A propensity-matched analysis, meta-analysis, and meta-regression analysis, along with additional observational studies, have demonstrated that combination therapy produces a superior clinical outcome in severely ill, septic patients with a high risk of death (86–90). In light of the increasing frequency of resistance to antimicrobial agents in many parts of the world, broad-spectrum coverage generally requires the initial use of combinations of antimicrobial agents. Combination therapy used in this context connotes at least two different classes of antibiotics (usually a beta-lactam agent with a macrolide, fluoroquinolone, or aminoglycoside for select patients). A controlled trial suggested, however, that when using a carbapenem as empiric therapy in a population at low risk for infection with resistant microorganisms, the addition of a fluoroquinolone does not improve outcomes of patients (85). A number of other recent observational studies and some small, prospective trials support initial combination therapy for selected patients with specific pathogens (eg, pneumococcal sepsis, multidrug-resistant Gram-negative pathogens) (91–93), but evidence from adequately powered, randomized clinical trials is not available to support combination over monotherapy other than in septic patients at high risk of death. In some clinical scenarios, combination therapies are biologically plausible and are likely clinically useful even if evidence has not demonstrated improved clinical outcome (89, 90, 94, 95). Combination therapy for suspected or known *Pseudomonas aeruginosa* or other multidrug-resistant Gram-negative pathogens, pending susceptibility results, increases the likelihood that at least one drug is effective against that strain and positively affects outcome (88, 96).

5. We suggest that the duration of therapy typically be 7 to 10 days if clinically indicated; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections, or immunologic deficiencies, including neutropenia (grade 2C).

Rationale. Although patient factors may influence the length of antibiotic therapy, in general, a duration of 7-10 days (in the absence of source control issues) is adequate. Thus, decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information. Clinicians should be cognizant of blood cultures being negative in a significant percentage of cases of severe sepsis or septic shock, despite the fact that many of these cases are very likely caused by bacteria or fungi. Clinicians should be cognizant that blood cultures will be negative in a significant percentage of cases of severe sepsis or septic shock, despite many of these cases are very likely caused by bacteria or fungi.

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

Rationale. Recommendations for antiviral treatment include the use of: a) early antiviral treatment of suspected or confirmed influenza among persons with severe influenza (eg, those who have severe, complicated, or progressive illness or who require hospitalization); b) early antiviral treatment of suspected or confirmed influenza among persons at higher risk for influenza complications; and c) therapy with a neuraminidase inhibitor (oseltamivir or zanamivir) for persons with influenza caused by 2009 H1N1 virus, influenza A (H3N2) virus, or influenza B virus, or when the influenza virus type or influenza A virus subtype is unknown (97, 98). Susceptibility to antivirals is highly variable in a rapidly evolving virus such as influenza, and therapeutic decisions must be guided by updated information regarding the most active, strain-specific, antiviral agents during influenza epidemics (99, 100).

The role of cytomegalovirus (CMV) and other herpesviruses as significant pathogens in septic patients, especially those not known to be severely immunocompromised, remains unclear. Active CMV viremia is common (15%–35%) in critically ill patients; the presence of CMV in the bloodstream has been repeatedly found to be a poor prognostic indicator (101, 102). What is not known is whether CMV simply is a marker of disease severity or if the virus actually contributes to organ injury and death in septic patients (103). No treatment recommendations can be given based on the current level of evidence. In those patients with severe primary or generalized varicella-zoster virus infections, and in rare patients with disseminated herpes simplex infections, antiviral agents such as acyclovir can be highly effective when initiated early in the course of infection (104).

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

Rationale. When infection is found not to be present, antimicrobial therapy should be stopped promptly to minimize the likelihood that the patient will become infected with an antimicrobial-resistant pathogen or will develop a drug-related adverse effect. Although it is important to stop unnecessary antibiotics early, clinicians should be cognizant that blood cultures will be negative in more than 50% of cases of severe sepsis or septic shock if the patients are receiving empiric antimicrobial therapy; 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.

E. Source Control

1. We recommend that a specific anatomical diagnosis of infection requiring consideration for emergent source control (eg, necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).
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. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

Rationale. The principles of source control in the management of sepsis include a rapid diagnosis of the specific site of infection and identification of a focus of 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) (105). 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 (106–108), and intravascular access devices that are potentially the source of severe sepsis or septic shock should be removed promptly after establishing other sites for vascular access (109, 110).

A randomized, controlled trial (RCT) comparing early to delayed surgical intervention for peripancreatic necrosis showed better outcomes with a delayed approach (111). Moreover, a randomized surgical study found that a minimally invasive, step-up approach was better tolerated by patients and had a lower mortality than open necrosectomy in necrotizing pancreatitis (112), although areas of uncertainty exist, such as definitive documentation of infection and appropriate length of delay. The selection of optimal source control methods must weigh the benefits and risks of the specific intervention as well as risks of transfer (113). Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. Surgical intervention should be considered when other interventional approaches are inadequate or when diagnostic uncertainty persists despite radiologic evaluation. Specific clinical situations require consideration of available choices, the patient's preferences, and the clinician's expertise.

F. Infection Prevention

1a. We suggest that selective oral decontamination (SOD) and selective digestive decontamination (SDD) should be introduced and investigated as a method to reduce the

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

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

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

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

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

Hemodynamic Support and Adjunctive Therapy (Table 6)

G. Fluid Therapy of Severe Sepsis

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

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

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

The SAFE study indicated that albumin administration was safe and equally as effective as 0.9% saline (129). A meta-analysis aggregated data from 17 randomized trials ($n = 1977$) of albumin vs. other fluid solutions in patients with severe sepsis/septic shock (130); 279 deaths occurred among 961 albumin-treated patients vs. 343 deaths among 1.016 patients treated with other fluids, thus favoring albumin (odds ratio [OR], 0.82; 95% CI, 0.67–1.00; $I^2 = 0\%$). When albumin-treated patients were compared

TABLE 6. Recommendations: Hemodynamic Support and Adjunctive Therapy

G. Fluid Therapy of Severe Sepsis

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

H. Vasopressors

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

I. Inotropic Therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids

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

with those receiving crystalloids (seven trials, $n = 1441$), the OR of dying was significantly reduced for albumin-treated patients (OR, 0.78; 95% CI, 0.62–0.99; $I^2 = 0\%$). A multicenter randomized trial ($n = 794$) in patients with septic shock compared intravenous albumin (20 g, 20%) every 8 hrs for 3 days to intravenous saline solution (130); albumin therapy was associated with 2.2% absolute reduction in 28-day mortality (from 26.3% to 24.1%), but did not achieve statistical significance. These data support a low-level recommendation regarding the use of albumin in patients with sepsis and septic shock (personal communication from J.P. Mira and as presented at the 32nd International ISICEM Congress 2012, Brussels and the 25th ESICM Annual Congress 2012, Lisbon).

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

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

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

H. Vasopressors

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

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

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

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

TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

Norepinephrine compared with dopamine in severe sepsis

Patient or population: Patients with severe sepsis
Settings: Intensive care unit
Intervention: Norepinephrine
Comparison: Dopamine
Sources: Analysis performed by Djillali Annane for Surviving Sepsis Campaign using following publications: De Backer D. *N Engl J Med* 2010; 362:779–789; Marik PE. *JAMA* 1994; 272:1354–1357; Mathur RDAC. *Indian J Crit Care Med* 2007; 11:186–191; Martin C. Chest 1993; 103:1826–1831; Patel GP. *Shock* 2010; 33:375–380; Ruokonen E. *Crit Care Med* 1993; 21:1296–1303

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	

[a]The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval, RR = risk ratio.

[b]Strong heterogeneity in the results ($I^2 = 85\%$), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

[c]Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.

arrhythmias, these were more frequent with dopamine than with norepinephrine (RR, 2.34 [1.46–3.77]; $p = 0.001$) (153).

Although some human and animal studies suggest epinephrine has deleterious effects on splanchnic circulation and produces hyperlactatemia, no clinical evidence shows that epinephrine results in worse outcomes, and it should be the first alternative to norepinephrine. Indeed, information from 4 randomized trials ($n = 540$) comparing norepinephrine to epinephrine found no evidence for differences in the risk of dying (RR, 0.96; CI, 0.77–1.21; fixed effect; $I^2 = 0\%$) (142, 147, 154, 155). Epinephrine may increase aerobic lactate production via stimulation of skeletal muscles' β_2-adrenergic receptors and thus may prevent the use of lactate clearance to guide resuscitation. With its almost pure α-adrenergic effects, phenylephrine is the adrenergic agent least likely to produce tachycardia, but it may decrease stroke volume and is therefore not recommended for use in the treatment of septic shock except in circumstances where norepinephrine is: a) associated with serious arrhythmias, or b) cardiac output is known to be high, or c) as salvage therapy when other vasopressor agents have failed to achieve target MAP (156). Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (157). Low doses of vasopressin may be effective in raising blood pressure in patients, refractory to other vasopressors and may have other potential physiologic benefits (158–163). Terlipressin has similar effects but is long acting (164). Studies show that vasopressin concentrations are elevated in early septic shock, but decrease to normal range in the majority of patients between 24 and 48 hrs as shock continues (165). 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 VASST trial, an RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min, showed no difference in outcome in the intent-to-treat population (166). An a priori defined subgroup analysis demonstrated that survival among patients receiving < 15 μg/min norepinephrine at the time of randomization was better with the addition of vasopressin; however, the pretrial rationale for this stratification was based on exploring potential benefit in the population requiring ≥ 15 μg/min norepinephrine. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed (167). Information from seven trials ($n = 963$ patients with septic shock) comparing norepinephrine with vasopressin (or terlipressin) does not support the routine use of vasopressin or its analog terlipressin (93, 95, 97, 99, 159, 161, 164, 166, 168–170). Indeed, the relative risk of dying was 1.12 (95% CI, 0.96–1.30; fixed effects; $I^2 = 0\%$). However, the risk of supraventricular arrhythmias was increased with norepinephrine (RR, 7.25; 95% CI, 2.30–22.90; fixed effect;

$I^2 = 0\%$). Cardiac output measurement targeting maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.

8. 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) (171, 172). Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function.

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

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.

I. Inotropic Therapy

1. We recommend that a trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of: a) myocardial dysfunction, as suggested by elevated cardiac filling pressures and low cardiac output, or b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. 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 MAP. 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 epinephrine, 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 MAP and cardiac output. Large prospective clinical trials, which included critically ill ICU patients who had severe sepsis, failed to demonstrate benefit from increasing oxygen delivery to supranormal targets by use of dobutamine (173, 174). These studies did not specifically target patients with severe sepsis and did not target the first 6 hrs of resuscitation. If evidence of tissue hypoperfusion persists despite adequate intravascular volume and adequate MAP, a viable alternative (other than reversing underlying insult) is to add inotropic therapy.

J. Corticosteroids

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

Rationale. The response of septic shock patients to fluid and vasopressor therapy seems to be an important factor in selection of patients for optional hydrocortisone therapy. One French multicenter RCT of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors for more than 60 mins) showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as postadrenocorticotropic hormone [ACTH] cortisol increase ≤ 9 μg/dL) (175). Two smaller RCTs also showed significant effects on shock reversal with steroid therapy (176, 177). In contrast, a large, European multicenter trial (CORTICUS) that enrolled patients without sustained shock and had a lower risk of death than the French trial failed to show a mortality benefit with steroid therapy (178). Unlike the French trial that 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; the study baseline (placebo) 28-day mortality rate was 61% and 31%, respectively. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. In recent years, several systematic reviews have examined the use of low-dose hydrocortisone in septic shock with contradictory results: Annane et al (179) analyzed the results of 12 studies and calculated a significant reduction in 28-day mortality with prolonged low-dose steroid treatment in adult septic shock patients (RR, 0.84; 95% CI, 0.72–0.97; $p = 0.02$) (180). In parallel, Sligl and colleagues (180) used a similar technique, but only identified eight studies for their meta-analysis, six of which had a high-level RCT design with low risk of bias (181). In contrast to the aforementioned review, this analysis revealed no statistically significant difference in mortality (RR, 1.00; 95% CI, 0.84–1.18). Both reviews, however, confirmed the improved shock reversal by using low-dose hydrocortisone (180, 181). A recent review on the use of steroids in adult septic shock underlined the importance of selection of studies for systematic analysis (181) and identified only 6 high-level RCTs as adequate for systematic review (175–178, 182, 183). When only these six studies are analyzed, we found that in "low risk" patients from three studies (ie, those with a placebo mortality rate of less than 50%, which represents the majority of all patients), hydrocortisone failed to show any benefit on outcome (RR, 1.06). The minority of patients from the remaining three studies, who had a placebo mortality of greater than 60%, showed a nonsignificant trend to lower mortality by using hydrocortisone (see **Supplemental Digital Content 4**, http://links.lww.com/CCM/A615, Summary of Evidence Table).

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

Rationale. In one study, the observation of a potential interaction between steroid use and ACTH test was not statistically significant (175). Furthermore, no evidence of this distinction was observed between responders and nonresponders in a recent multicenter trial (178). Random cortisol levels may still be useful for absolute adrenal insufficiency; however, for septic shock patients who suffer from relative adrenal insufficiency (no adequate stress response), random cortisol levels have not been demonstrated to be useful. Cortisol immunoassays may over- or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders (184). 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 (185, 186). Moreover, a subanalysis of the CORTICUS trial (178) revealed that the use of etomidate before application of low-dose steroids was associated with an increased 28-day mortality rate (187). An inappropriately low random cortisol level (< 18 μg/dL) in a patient with shock would be considered an indication for steroid therapy along traditional adrenal insufficiency guidelines.

3. We suggest that clinicians taper the treated 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 (175, 177, 178), and therapy was decreased after shock resolution in two RCTs (176, 182). In four studies, steroids were tapered over several days (176–178, 182), and steroids were withdrawn abruptly in two RCTs (175, 183). One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids (188). Furthermore, a study revealed that there is no difference in outcome of septic shock patients if low-dose hydrocortisone is used for 3 or 7 days; hence, no recommendation can be given with regard to the optimal duration of hydrocortisone therapy (189).

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

Rationale. Steroids may be indicated in the presence of a history of steroid therapy or adrenal dysfunction, but whether low-dose steroids have a preventive potency in reducing the incidence of severe sepsis and septic shock in critically ill patients cannot be answered. A preliminary study of stress-dose level steroids in community-acquired pneumonia showed improved outcome measures in a small population (190), and a recent confirmatory RCT revealed reduced hospital length of stay without affecting mortality (191).

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

Rationale. Several randomized trials on the use of low-dose hydrocortisone in septic shock patients revealed a significant increase of hyperglycemia and hypernatremia (175) as side effects. A small prospective study demonstrated that repetitive bolus application of hydrocortisone leads to a significant increase in blood glucose; this peak effect was not detectable during continuous infusion. Furthermore, considerable interindividual variability was seen in this blood glucose peak after the hydrocortisone bolus (192). Although an association of hyperglycemia and hypernatremia with patient outcome measures could not be shown, good practice includes strategies for avoidance and/or detection of these side effects.

SUPPORTIVE THERAPY OF SEVERE SEPSIS (TABLE 8)

K. Blood Product Administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, we recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to < 7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL in adults (grade 1B).

Rationale. Although the optimum hemoglobin concentration for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin level of 7 to 9 g/dL, compared with 10 to 12 g/dL, was not associated with increased mortality in critically ill adults (193). No significant differences in 30-day mortality rates were observed between treatment groups in the subgroup of patients with severe infections and septic shock (22.8% and 29.7%, respectively; $p = 0.36$),

Although less applicable to septic patients, results of a randomized trial in patients undergoing cardiac surgery with cardiopulmonary bypass support a restrictive transfusion strategy using a threshold hematocrit of < 24% (hemoglobin ≈8 g/dL) as equivalent to a transfusion threshold of hematocrit of < 30% (hemoglobin ≈10 g/dL) (194). Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption (195–197). The transfusion threshold of 7 g/dL contrasts with early goal-directed resuscitation protocols that use a target hematocrit of 30% in patients with low Scv_{O_2} during the first 6 hrs of resuscitation of septic shock (13).

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

Rationale. No specific information regarding erythropoietin use in septic patients is available, but clinical trials of erythropoietin administration in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome (198, 199). 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 meet indications for the 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 it 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 (200–203). In addition, transfusion of fresh frozen plasma usually fails to correct the prothrombin time in nonbleeding patients with mild abnormalities (204, 205). No studies 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 (206). Although a post hoc subgroup analysis of patients with severe sepsis and high risk of death showed better survival in patients receiving antithrombin, this agent cannot be recommended until further clinical trials are performed (207).

5. In patients with severe sepsis, we suggest that platelets be administered prophylactically when counts are ≤ 10,000/mm^3 (10×10^9/L) in the absence of apparent bleeding, as well when counts are ≤ 20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 [50×10^9/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

Rationale. Guidelines for transfusion of platelets are derived from consensus opinion and experience in patients with chemotherapy-induced thrombocytopenia. Patients with severe sepsis are likely to have some limitation of platelet production similar to that in chemotherapy-treated patients, but they also are likely to have increased platelet consumption. Recommendations take into account the etiology of thrombocytopenia, platelet dysfunction, risk of bleeding, and presence of concomitant disorders (200, 202, 203, 208, 209). Factors that may increase the bleeding risk and indicate the need for a higher platelet count are frequently present in patients with severe sepsis. Sepsis itself is considered to be a risk factor for bleeding in patients with chemotherapy-induced thrombocytopenia. Other factors considered to increase the risk of bleeding in patients with severe sepsis include temperature higher than 38°C, recent minor hemorrhage, rapid decrease in platelet count, and other coagulation abnormalities (203, 208, 209).

L. Immunoglobulins

1. We suggest not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).

Rationale. One larger multicenter RCT (n = 624) (210) in adult patients and one large multinational RCT in infants with neonatal sepsis (n = 3493) (211) found no benefit for intravenous immunoglobulin (IVIG). (For more on this trial, see the section, Pediatric Considerations.). A meta-analysis by the Cochrane collaboration, which did not include this most recent RCT, identified 10 polyclonal IVIG trials (n = 1430) and seven trials on immunoglobulin (Ig) M-enriched polyclonal IVIG (n = 528) (212). Compared with placebo, IVIG resulted in a significant reduction in mortality (RR, 0.81 and 95% CI, 0.70–0.93; and RR, 0.66 and 95% CI, 0.51–0.85, respectively). Also the subgroup of IgM-enriched IVIGs (n = 7 trials) showed a significant reduction in mortality rates compared with placebo (RR, 0.66; 95% CI, 0.51–0.85). Trials with low risk of bias showed no reduction in mortality with polyclonal IVIG (RR, 0.97; 95% CI, 0.81–1.15; five trials, n = 945). Three of these trials (210, 213, 214) used standard polyclonal IVIG and two IgM-enriched IVIG (215, 216).

These findings are in accordance with those of two older meta-analyses (217, 218) from other Cochrane authors. One systematic review (217) included a total of 21 trials and showed a relative risk of death of 0.77 with immunoglobulin treatment (95% CI, 0.68–0.88); however, the results of only high-quality trials (total of 763 patients) showed a relative risk of 1.02 (95% CI, 0.84–1.24). Similarly, Laupland et al (218) found a significant reduction in mortality with the use of IVIG treatment (OR, 0.66; 95% CI, 0.53–0.83; $p < 0.005$). When only high-quality studies were pooled, the OR for mortality was 0.96 (95% CI, 0.71–1.3; $p = 0.78$). Two meta-analyses, which used less strict criteria to identify sources of bias or did not state their criteria for the assessment of study quality, found significant improvement in patient mortality with IVIG treatment (219, 220). In contrast to the most recent Cochrane review, Kreymann et al (219) classified five studies that investigated IgM-enriched preparation as high-quality studies, combining studies in adults and neonates, and found an OR for mortality of 0.5 (95% CI, 0.34–0.73).

Most IVIG studies are small, some have methodological flaws; the only large study (n = 624) showed no effect (210). Subgroup effects between IgM-enriched and nonenriched formulations reveal substantial heterogeneity. In addition, indirectness and publication bias were considered in grading this recommendation. The low-quality evidence led to the grading as a weak recommendation. The statistical information that comes from the high-quality trials does not support a beneficial effect of polyclonal IVIG. We encourage conducting large multicenter studies to further evaluate the effectiveness of other polyclonal immunoglobulin preparations given intravenously in patients with severe sepsis.

M. Selenium

1. We suggest not using intravenous selenium to treat severe sepsis (grade 2C).

TABLE 8. Recommendations: Other Supportive Therapy of Severe Sepsis

K. Blood Product Administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease, we recommend that red blood cell transfusion occur only when hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 –9.0 g/dL in adults (grade 1B).
2. Not using erythropoietin as a specific treatment of anemia associated with severe sepsis (grade 1B).
3. Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).
4. Not using antithrombin for the treatment of severe sepsis and septic shock (grade 1B).
5. In patients with severe sepsis, administer platelets prophylactically when counts are <10,000/mm^3 (10 x 10^9/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are < 20,000/mm^3 (20 x 10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3 [50 x 10^9/L]) are advised for active bleeding, surgery, or invasive procedures (grade 2D).

L. Immunoglobulins

1. Not using intravenous immunoglobulins in adult patients with severe sepsis or septic shock (grade 2B).

M. Selenium

1. Not using intravenous selenium for the treatment of severe sepsis (grade 2C).

N. History of Recommendations Regarding Use of Recombinant Activated Protein C (rhAPC)

A history of the evolution of SSC recommendations as to rhAPC (no longer available) is provided.

O. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)

1. Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A vs. 12 mL/kg).
2. Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H_2O (grade 1B).
3. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
4. Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis- induced moderate or severe ARDS (grade 2C).
5. Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia (grade 2C).
6. Prone positioning be used in sepsis-induced ARDS patients with a Pao_2/Fio_2 ratio ≤ 100 mm Hg in facilities that have experience with such practices (grade 2B).
7. That mechanically ventilated sepsis patients be maintained with the head of the bed elevated to 30-45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).
8. That noninvasive mask ventilation (NIV) be used in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (grade 2B).
9. 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) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low Fio_2 requirements which can be met safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (grade 1A).
10. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).
11. A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).
12. In the absence of specific indications such as bronchospasm, not using beta 2-agonists for treatment of sepsis-induced ARDS (grade 1B).

P. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. Continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints (grade 1B).
2. Neuromuscular blocking agents (NMBAs) be avoided if possible in the septic patient *without ARDS* due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).

(*Continued*)

TABLE 8. (*Continued*) Recommendations: Other Supportive Therapy of Severe Sepsis

3. A short course of NMBA of not greater than 48 hours for patients *with* early sepsis-induced ARDS and a Pao_2/Fio_2 < 150 mm Hg (grade 2C).

Q. Glucose Control

1. A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose ≤180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (grade 1A).
2. 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).
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

R. Renal Replacement Therapy

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

S. Bicarbonate Therapy

1. Not using sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (grade 2B).

T. Deep Vein Thrombosis Prophylaxis

1. Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). This should be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus twice daily UFH, grade 2C versus three times daily UFH). If creatinine clearance is <30 mL/min, use dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).
2. Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
3. Septic patients who have a contraindication for heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not receive pharmacoprophylaxis (grade 1B), but receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases start pharmacoprophylaxis (grade 2C).

U. Stress Ulcer Prophylaxis

1. Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).
2. When stress ulcer prophylaxis is used, proton pump inhibitors rather than H2RA (grade 2D)
3. Patients without risk factors do not receive prophylaxis (grade 2B).

V. Nutrition

1. Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock (grade 2C).
2. Avoid mandatory full caloric feeding in the first week but rather suggest low dose feeding (eg, up to 500 calories per day), advancing only as tolerated (grade 2B).
3. Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).
4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

W. Setting Goals of Care

1. Discuss goals of care and prognosis with patients and families (grade 1B).
2. Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B).
3. Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (grade 2C).

Rationale. Selenium was administered in the hope that it could correct the known reduction of selenium concentration in sepsis patients and provide a pharmacologic effect through an antioxidant defense. Although some RCTs are available, the evidence on the use of intravenous selenium is still very weak. Only one large clinical trial has examined the effect on mortality rates, and no significant impact was reported on the intent-to-treat population with severe systemic inflammatory response syndrome, sepsis, or septic shock (OR, 0.66; 95% CI, 0.39–1.10; $p = 0.109$) (221). Overall, there was a trend toward a concentration-dependent reduction in mortality; no differences in secondary outcomes or adverse events were detected. Finally, no comment on standardization of sepsis management was included in this study, which recruited 249 patients over a period of 6 years (1999–2004) (221).

A French RCT in a small population revealed no effect on primary (shock reversal) or secondary (days on mechanical ventilation, ICU mortality) endpoints (222). Another small RCT revealed less early VAP in the selenium group ($p = 0.04$), but no difference in late VAP or secondary outcomes such as ICU or hospital mortality (223). This is in accordance with two RCTs that resulted in reduced number of infectious episodes (224) or increase in glutathione peroxidase concentrations (225); neither study, however, showed a beneficial effect on secondary outcome measures (renal replacement, ICU mortality) (224, 225).

A more recent large RCT tried to determine if the addition of relatively low doses of supplemental selenium (glutamine was also tested in a two-factorial design) to parenteral nutrition in critically ill patients reduces infections and improves outcome (226). Selenium supplementation did not significantly affect the development of a new infection (OR, 0.81; 95% CI, 0.57–1.15), and the 6-month mortality rate was not unaffected (OR, 0.89; 95% CI, 0.62–1.29). In addition, length of stay, days of antibiotic use, and modified Sequential Organ Failure Assessment score were not significantly affected by selenium (227).

In addition to the lack of evidence, the questions of optimal dosing and application mode remain unanswered. Reported high-dose regimens have involved a loading dose followed by an infusion, while animal trials suggest that bolus dosing could be more effective (227); this, however, has not been tested in humans. These unsolved problems require additional trials, and we encourage conducting large multicenter studies to further evaluate the effectiveness of intravenous selenium in patients with severe sepsis. This recommendation does not exclude the use of low-dose selenium as part of the standard minerals and oligo-elements used during total parenteral nutrition.

N. History of Recommendations Regarding Use of Recombinant Activated Protein C

Recombinant human activated protein C (rhAPC) was approved for use in adult patients in a number of countries in 2001 following the PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial, which enrolled 1,690 severe sepsis patients and showed a significant reduction in mortality (24.7%) with rhAPC compared with placebo (30.8%, $p = 0.005$) (228). The 2004 SSC guidelines recommended use of rhAPC in line with the product labeling instructions required by the U.S. and European regulatory authorities with a grade B quality of evidence (7, 8).

By the time of publication of the 2008 SSC guidelines, additional studies of rhAPC in severe sepsis (as required by regulatory agencies) had shown it ineffective in less severely ill patients with severe sepsis as well as in children (229, 230). The 2008 SSC recommendations reflected these findings, and the strength of the rhAPC recommendation was downgraded to a suggestion for use in adult patients with a clinical assessment of high risk of death, most of whom will have Acute Physiology and Chronic Health Evaluation (APACHE) II scores ≥ 25 or multiple organ failure (grade 2C; quality of evidence was also downgraded from 2004, from B to C) (7). The 2008 guidelines also recommended against use of rhAPC in low-risk adult patients, most of whom will have APACHE II scores ≤ 20 or single organ failures (grade 1A), and against use in all pediatric patients (grade 1B).

The results of the PROWESS SHOCK trial (1,696 patients) were released in late 2011, showing no benefit of rhAPC in patients with septic shock (mortality 26.4% for rhAPC, 24.2% placebo) with a relative risk of 1.09 and a p value of 0.31 (231). The drug was withdrawn from the market and is no longer available, negating any need for an SSC recommendation regarding its use.

O. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome

1. We recommend that clinicians target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (ARDS) (grade 1A vs. 12 mL/kg).
2. We recommend that plateau pressures be measured in patients with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated lung be ≤ 30 cm H_2O (grade 1B).

Rationale. Of note, studies used to determine recommendations in this section enrolled patients using criteria from the American-European Consensus Criteria Definition for Acute Lung Injury (ALI) and ARDS (232). For this document, we have used the updated Berlin definition and used the terms *mild, moderate,* and *severe ARDS* (Pao_2/Fio_2 ≤300, ≤200, and ≤100 mm Hg, respectively) for the syndromes previously known as ALI and ARDS (233). Several multicenter randomized trials have been performed in patients with established ARDS to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume (234–238). These studies showed differing results that may have been caused by differences in airway pressures in the treatment and control groups (233, 234, 239). Several meta-analyses suggest decreased mortality in patients with a pressure- and volume-limited strategy for established ARDS (240, 241).

The largest trial of a volume- and pressure-limited strategy showed an absolute 9% decrease in all-cause mortality in patients with ARDS ventilated with tidal volumes of 6 mL/kg compared with 12 mL/kg of predicted body weight (PBW), and aiming for a plateau pressure ≤ 30 cm H_2O (233). The use of lung-protective

strategies for patients with ARDS is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ARDS 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. Patients with profound metabolic acidosis, high obligate minute ventilations, or short stature may require additional manipulation of tidal volumes. 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 (242, 243). The validity of this ceiling value will depend on the patient's effort, as those who are actively breathing generate higher transalveolar pressures for a given plateau pressure than patients who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures > 30 cm H_2O to meet vital clinical objectives. A retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤ 30 cm H_2O (244) as lower plateau pressures were associated with decreased in-hospital mortality (245).

High tidal volumes that are coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1 to 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 the plateau pressure remains > 30 cm H_2O after reduction of tidal volume to 6 mL/kg PBW, tidal volume may be reduced further to as low as 4 mL/kg PBW per protocol. (**Appendix C** provides ARDSNet ventilator management and formulas to calculate PBW.) Using volume- and pressure-limited ventilation may lead to hypercapnia with maximum tolerated set respiratory rates. In such cases, hypercapnia that is otherwise not contraindicated (eg, high intracranial pressure) and appears to be tolerated should be allowed. Sodium bicarbonate or tromethamine (THAM) infusion may be considered in selected patients to facilitate use of limited ventilator conditions that result in permissive hypercapnia (246, 247).

A number of observational trials in mechanically ventilated patients have demonstrated a decreased risk of developing ARDS when smaller trial volumes are used (248–251). Accordingly, high tidal volumes and plateau pressures should be avoided in mechanically ventilated patients at risk for developing ARDS, including those with sepsis.

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

3. We recommend that positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).

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

Rationale. Raising PEEP in ARDS keeps lung units open to participate in gas exchange. This will increase Pa_{O_2} when PEEP is applied through either an endotracheal tube or a face mask (252–254). In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury when relatively high plateau pressures are in use. Three large multicenter trials using higher vs. lower levels of PEEP in conjunction with low tidal volumes did not uncover benefit or harm (255–257). A meta-analysis using individual patient data showed no benefit in all patients with ARDS; however, patients with moderate or severe ARDS (Pa_{O_2}/F_{IO_2} ratio ≤ 200 mm Hg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not (258). 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 (259). The second option is to titrate PEEP based on severity of oxygenation deficit and guided by the F_{IO_2} required to maintain adequate oxygenation (234, 255, 256). A PEEP > 5 cm H_2O is usually required to avoid lung collapse (260). The ARDSNet standard PEEP strategy is shown in Appendix C. The higher PEEP strategy recommended for ARDS is shown in **Appendix D** and comes from the ALVEOLI trial (257).

5. We suggest recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (grade 2C).

6. We suggest prone positioning in sepsis-induced ARDS patients with a Pa_{O_2}/F_{IO_2} ratio ≤ 100 mm Hg in facilities that have experience with such practices (grade 2B).

Rationale. Many strategies exist for treating refractory hypoxemia in patients with severe ARDS (261). Temporarily raising transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange (260), but could also overdistend aerated lung units leading to ventilator-induced lung injury and temporary hypotension. The application of transient sustained use of continuous positive airway pressure appears to improve oxygenation in patients initially, but these effects can be transient (262). Although selected patients with severe hypoxemia may benefit from recruitment maneuvers in conjunction with higher levels of PEEP, little evidence supports the routine use in all ARDS patients (262). Blood pressure and oxygenation should be monitored and recruitment maneuvers discontinued if deterioration in these variables is observed.

Several small studies and one large study in patients with hypoxemic respiratory failure or ARDS have shown that most patients respond to the prone position with improved oxygenation (263–266). None of the individual trials of prone positioning in patients with ARDS or hypoxemic respiratory failure demonstrated a mortality benefit (267–270). One meta-analysis suggested potential benefits for prone positioning in patients with profound hypoxemia and Pa_{O_2}/F_{IO_2} ratio ≤ 100 mm Hg, but not in those with less severe hypoxemia (270). Prone positioning may be associated with potentially life-threatening complications, including accidental dislodging of the endotracheal

and chest tubes; these complications occur more frequently in patients in the prone compared with supine position (270).

Other methods to treat refractory hypoxemia, including high-frequency oscillatory ventilation, airway pressure release ventilation, and extracorporeal membrane oxygenation (271), may be considered as rescue therapies in centers with expertise and experience with their use (261, 271–274). Inhaled nitric oxide does not improve mortality rates in patients with ARDS and should not be routinely used (275).

7. We recommend that mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP (grade 1B).

Rationale. The semi-recumbent position has been demonstrated to decrease the incidence of VAP (276). Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed enterally in the supine position developed VAP compared with 9% of those fed in the semi-recumbent position (276). However, the bed position was monitored only once a day, and patients who did not achieve the desired bed elevation were not included in the analysis (276). One study did not show a difference in incidence of VAP between patients maintained in supine and semi-recumbent positions (277); patients assigned to the semi-recumbent group 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 semi-recumbent group by day 7 (277). When necessary, patients may be laid flat for procedures, hemodynamic measurements, and during episodes of hypotension. Patients should not be fed enterally while supine.

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

Rationale. Obviating the need for airway intubation confers multiple advantages: better communication, lower incidence of infection, and reduced requirements for sedation. Two RCTs in patients with acute respiratory failure demonstrated improved outcome with the use of NIV when it can be used successfully (278, 279). Unfortunately, only a small percentage of sepsis patients with life-threatening hypoxemia can be managed in this way (280, 281).

NIV should be considered in patients with sepsis-induced ARDS if they are responsive to relatively low levels of pressure support and PEEP with stable hemodynamics, can be made comfortable, and are easily arousable; if they are able to protect the airway and spontaneously clear the airway of secretions; and if they are anticipated to recover rapidly from the precipitating insult (280, 281). A low threshold for airway intubation should be maintained.

9. 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) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low F_{IO_2} requirements which can be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, extubation should be considered (grade 1A).

Rationale. Spontaneous breathing trial options include a low level of pressure support, continuous positive airway pressure (≈5 cm H_2O), or a use of a T-piece. Studies demonstrated that daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation (282, 283). These breathing trials should be conducted in conjunction with a spontaneous awakening trial (284). Successful completion of spontaneous breathing trials leads to a high likelihood of successful early discontinuation of mechanical ventilation.

10. We recommend against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (grade 1A).

Rationale. Although insertion of a pulmonary artery (PA) catheter may provide useful information on a patient's volume status and cardiac function, these benefits may be confounded by differences in the interpretation of results (285–287), lack of correlation of PA occlusion pressures with clinical response (288), and an absence of a proven strategy to use catheter results to improve patient outcomes (173). Two multicenter randomized trials, one in patients with shock or ARDS (289) and the other in those with only ARDS (290), failed to show benefit with the routine use of PA catheters in ARDS. In addition, other studies in different types of critically ill patients have failed to show definitive benefit with routine use of the PA catheter (291–293). Well-selected patients remain appropriate candidates for PA catheter insertion only when the answers to important management decisions depend on information solely obtainable from direct measurements made within the PA (292, 294).

11. We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (grade 1C).

Rationale. Mechanisms for the development of pulmonary edema in patients with ARDS include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure (295). Small prospective studies in patients with critical illness and ARDS have suggested that low weight gain is associated with improved oxygenation (296) and fewer days of mechanical ventilation (297, 298). A fluid-conservative strategy to minimize fluid infusion and weight gain in patients with ARDS, based on either a central venous catheter (CVP < 4 mm Hg) or a PA catheter (pulmonary artery wedge pressure < 8 mm Hg), along with clinical variables to guide treatment, led to fewer days of mechanical ventilation and reduced length of ICU stay without altering the incidence of renal failure or mortality rates (299). This strategy was only used in patients

with established ARDS, some of whom had shock present during the ICU stay, and active attempts to reduce fluid volume were conducted only outside periods of shock.

12. In the absence of specific indications such as bronchospasm, we recommend against the use of β_2-agonists for treatment of patients with sepsis-induced ARDS (grade 1B).

Rationale. Patients with sepsis-induced ARDS often develop increased vascular permeability. Preclinical and early clinical data suggest that β-adrenergic agonists may speed resorption of alveolar edema (300). Two randomized clinical trials studied the effect of β-agonists in patients with ARDS (301, 302). In one, a comparison of aerosolized albuterol and placebo in 282 patients with ARDS, the trial was stopped for futility (301). Patients receiving albuterol had higher heart rates on day 2, and a trend was detected toward decreased ventilator-free days (days alive and off the ventilator). The rates of death before discharge were 23.0% in the albuterol group vs. 17.7% in placebo-treated patients. More than half of the patients enrolled in this trial had pulmonary or nonpulmonary sepsis as the cause of the ARDS (301).

The use of intravenous salbutamol was tested in the BALTI-2 trial (302). Three hundred twenty-six patients with ARDS, 251 of whom had pulmonary or nonpulmonary sepsis as cause, were randomized to intravenous salbutatmol, 15 μg/kg of ideal body weight, or placebo for up to 7 days. Patients treated with salbutamol had increased 28-day mortality rates (34% vs. 23%; RR, 1.4; 95% CI, 1.03–2.08) leading to early termination of the trial (302).

Beta-2 agonists may have specific indications, such as treatment of bronchospasm and hyperkalemia. In the absence of these conditions, we recommend against the routine use of β-agonists, either in intravenous or aerosolized form, for the treatment of patients with sepsis-induced ARDS.

P. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

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

Rationale. A growing body of evidence indicates that limiting the use of sedation in critically ill ventilated patients can reduce the duration of mechanical ventilation and ICU and hospital lengths of stay (303–305). While studies limiting sedation have been performed in a wide range of critically ill patients, there is little reason to assume that septic patients will not derive benefit from this approach (305). The use of protocols for sedation is one method to limit sedation use, and a randomized, controlled clinical trial found that protocolized sedation compared with usual care reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates (305). Avoidance of sedation is another strategy. A recent observational study of 250 critically ill patients suggests that deep sedation is common in mechanically ventilated patients (306). A randomized, controlled clinical trial found that patients treated with intravenous morphine boluses preferentially had significantly more days without ventilation, shorter stay in ICU and hospital, than patients who received sedation (propofol and midazolam) in addition to morphine (307). However, agitated delirium was more frequently detected in the intervention group. Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily sedative interruption, and systematic titration to a predefined endpoint have been demonstrated to decrease the duration of mechanical ventilation (284, 305, 308, 309). Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because the neuromuscular blockade must first be reversed. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined in an observational study of mechanically ventilated patients that showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital lengths of stay (310).

Clinical trials have evaluated daily interruption of continuous sedative infusions. A prospective, randomized controlled trial 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 (283). 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. In addition, a paired spontaneous awakening trial combined with a spontaneous breathing trial decreased the duration of mechanical ventilation, length of ICU and hospital stay, and 1-year mortality (284). More recently, a multicenter randomized trial compared protocolized sedation with protocolized sedation plus daily sedation interruption in 423 critically ill mechanically ventilated medical and surgical patients (311). There were no differences in duration of mechanical ventilation or lengths of stay between the groups; and daily interruption was associated with higher daily opioid and benzodiazepines doses, as well as higher nurse workload. 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 (312). Regardless of sedation approach, early physical rehabilitation should be a goal (313).

2. We recommend that NMBAs be avoided if possible in the septic patient *without ARDS* due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (grade 1C).
3. We suggest a short course of an NMBA (≤ 48 hours) for patients *with* early, sepsis-induced ARDS and Pao_2/Fio_2 < 150 mm Hg (grace 2C).

Rationale. Although NMBAs are often administered to critically ill patients, their role in the ICU is not well defined. No evidence exists that 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 (314). When appropriately used, these agents may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures (315). Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow (316). 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 deep neuromuscular blockade (317).

A recent randomized clinical trial of continuous infusions of cisatracurium in patients with early ARDS and a Pa_{O_2}/F_{IO_2} < 150 mm Hg showed improved adjusted survival rates and more organ failure-free days without an increased risk in ICU-acquired weakness compared with placebo-treated patients (318). The investigators used a high fixed dose of cisatracurium without train-of-four monitoring, and half of the patients in the placebo group received at least a single dose of NMBA. Whether another NMBA would have similar effects is unknown. Although many of the patients enrolled into this trial appeared to meet sepsis criteria, it is not clear whether similar results would occur in sepsis patients. A GRADEpro Summary of Evidence Table regarding use of NMBA in ARDS appears in **Supplemental Digital Content 5** (http://links.lww.com/CCM/A615).

An association between NMBA use and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population (315, 319–322), but the mechanisms by which NMBAs produce or contribute to myopathies and neuropathies in these patients are unknown. Although no studies are specific to the septic patient population, it seems clinically prudent, based on existing 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 (315).

Only one prospective RCT has compared peripheral nerve stimulation and standard clinical assessment in ICU patients. Rudis et al (323) randomized 77 critically ill ICU patients requiring neuromuscular blockade to receive dosing of vecuronium based on train-of-four stimulation or on clinical assessment (control group). 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 (324, 325).

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.

Q. Glucose Control

1. We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL. This approach should target an upper blood glucose level ≤ 180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL (grade 1A).
2. We recommend blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter (grade 1C).
3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values (UG).

Rationale. One large RCT 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 to 110 mg/dL (326). A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU length of stay of more than 3 days in three medical ICUs and overall mortality was not reduced (327).

Since these studies (326, 327) and the previous Surviving Sepsis Guidelines (7) appeared, several RCTs (128, 328–332) and meta-analyses (333–337) of intensive insulin therapy have been performed. The RCTs studied mixed populations of surgical and medical ICU patients (128, 328–332) and found that intensive insulin therapy did not significantly decrease mortality (128, 328–332), whereas the NICE-SUGAR trial demonstrated an increased mortality (331). All studies (128, 326–332) reported a much higher incidence of severe hypoglycemia (glucose ≤ 40 mg/dL) (6%−29%) with intensive insulin therapy. Several meta-analyses confirmed that intensive insulin therapy was not associated with a mortality benefit in surgical, medical, or mixed ICU patients (333, 335, 337). The meta-analysis by Griesdale and colleagues (334), using between-trial comparisons driven mainly by the 2001 study by van den Berghe et al (326), found that intensive insulin therapy was beneficial in surgical ICU patients (risk ratio, 0.63 [0.44−0.9]), whereas the meta-analysis by Friedrich et al (336), using within-trial comparisons, showed no benefit for surgical patients in mixed medical-surgical ICUs (risk ratio 0.99 [0.82−1.11]) and no subgroup of surgical patients who benefited from intensive insulin therapy. Interestingly, the RCTs that reported (326, 327) compared intensive insulin therapy to high controls (180−200 mg/dL) (OR, 0.89 [0.73−1.09]), whereas those that did not demonstrate benefit (330–332) compared intensive therapy to moderate controls (108−180 mg/dL) [OR, 1.14 (1.02 to −1.26)]. See **Supplemental Digital Content 6** (http://links.lww.com/CCM/A615) for details.

The trigger to start an insulin protocol for blood glucose levels > 180 mg/dL with an upper target blood glucose level < 180 mg/dL derives from the NICE-SUGAR study (331), which used these values for initiating and stopping therapy. The

NICE-SUGAR trial is the largest, most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals and a general patient population. Several medical organizations, including the American Association of Clinical Endocrinologists, American Diabetes Association, American Heart Association, American College of Physicians, and Society of Critical Care Medicine, have published consensus statements for glycemic control of hospitalized patients (338–341). These statements usually targeted glucose levels between 140 and 180 mg/dL. As there is no evidence that targets between 140 and 180 mg/dL are different from targets of 110 to 140 mg/dL, the recommendations use an upper target blood glucose ≤ 180 mg/dL without a lower target other than hypoglycemia. Treatment should avoid hyperglycemia (> 180 mg/dL), hypoglycemia, and wide swings in glucose levels. The continuation of insulin infusions, especially with the cessation of nutrition, has been identified as a risk factor for hypoglycemia (332). Balanced nutrition may be associated with a reduced risk of hypoglycemia (342). Several studies have suggested that the variability in glucose levels over time is an important determinant of mortality (343–345). Hyperglycemia and glucose variability seem to be unassociated with increased mortality rates in diabetic patients compared to nondiabetic patients (346, 347).

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), Pa_{O_2}, and drugs (348). Plasma glucose values by capillary point-of-care testing have been found to be inaccurate with frequent false elevations (349, 350) over the range of glucose levels (350), but especially in the hypoglycemic (349, 351) and hyperglycemic ranges (351) and in hypotensive patients (352) or patients receiving catecholamines (353). A review of 12 published insulin infusion protocols for critically ill patients showed wide variability in dose recommendations and variable glucose control (354). 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 (eg, 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, conclusion supported by the wide variability in hypoglycemia rates reported with protocols (128, 326–333). Thus, the use of established insulin protocols is important not only for clinical care but also for the conduct of clinical trials to avoid hypoglycemia, adverse events, and premature termination of trials before the efficacy signal, if any, can be determined. Several studies have suggested that computer-based algorithms result in tighter glycemic control with a reduced risk of hypoglycemia (355, 356). Further study of validated, safe, and effective protocols for controlling blood glucose concentrations and variability in the severe sepsis population is needed.

R. Renal Replacement Therapy

1. We suggest that continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure because they achieve similar short-term survival rates (grade 2B).
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 (357–364), two meta-analyses (365, 366) 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 RCT studies (366). To date, five prospective RCTs have been published (367–371); four found no significant difference in mortality (368–371), whereas one found significantly higher mortality in the continuous treatment group (367), 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 (367). Most studies comparing modes of renal replacement in the critically ill have included a small number of patients and some major weaknesses (ie, randomization failure, modifications of therapeutic protocol during the study period, combination of different types of continuous renal replacement therapies, small number of heterogeneous groups of enrollees). The most recent and largest RCT (371) enrolled 360 patients and found no significant difference in survival between the continuous and intermittent groups. Moreover, no evidence supports the use of continuous therapies in sepsis independent of renal replacement needs.

No evidence supports a better tolerance with continuous treatments regarding the hemodynamic tolerance of each method. Two prospective studies (369, 372) have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion (372) and no survival benefit (369). Four other prospective studies did not find any significant difference in mean arterial pressure or drop in systolic pressure between the two methods (368, 370, 371, 373). Two studies reported a significant improvement in goal achievement with continuous methods (367, 369) regarding fluid balance management. In summary, the evidence is insufficient to draw strong conclusions regarding the mode of replacement therapy for acute renal failure in septic patients.

The effect of dose of continuous renal replacement on outcomes in patients with acute renal failure has shown mixed results (374, 375). None of these trials was conducted specifically in patients with sepsis. Although the weight of evidence suggests that higher doses of renal replacement may be associated with improved outcomes, these results may not be generalizable. Two large multicenter randomized trials comparing the dose of renal replacement (Acute Renal Failure Trial Network in the United States and RENAL Renal Replacement Therapy Study in Australia and New Zealand) failed to show benefit of more aggressive renal replacement dosing. (376, 377). A typical

dose for continuous renal replacement therapy would be 20 to 25 mL/kg/hr of effluent generation.

S. 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 ≥ 7.15 (grade 2B).

Rationale. Although bicarbonate therapy may be useful in limiting tidal volume in ARDS in some situations of permissive hypercapnia (see section, Mechanical Ventilation of ARDS), no evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidemia associated with sepsis. Two blinded, crossover RCTs that compared equimolar saline and bicarbonate in patients with lactic acidosis failed to reveal any difference in hemodynamic variables or vasopressor requirements (378, 379). The number of patients with < 7.15 pH 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.

T. Deep Vein Thrombosis Prophylaxis

1. We recommend that patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (grade 1B). We recommend that this be accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (grade 1B versus unfractionated heparin [UFH] twice daily and grade 2C versus UFH given thrice daily). If creatinine clearance is < 30 mL/min, we recommend use of dalteparin (grade 1A) or another form of LMWH that has a low degree of renal metabolism (grade 2C) or UFH (grade 1A).
2. We suggest that patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 2C).
3. We recommend that septic patients who have a contraindication to heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not receive pharmacoprophylaxis (grade 1B). Rather we suggest they receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (grade 2C), unless contraindicated. When the risk decreases, we suggest starting pharmacoprophylaxis (grade 2C).

Rationale. ICU patients are at risk for deep vein thrombosis (DVT) (380). It is logical that patients with severe sepsis would be at a similar or higher risk than the general ICU population. The consequences of VTE in the setting of sepsis (increased risk of potentially fatal pulmonary emboli in an already hemodynamically compromised patient) are dire. Therefore, prevention of VTE is highly desirable, especially if it can be done safely and effectively.

Prophylaxis is generally effective. In particular, nine placebo-controlled RCTs of VTE prophylaxis have been conducted in general populations of acutely ill patients (381–389). All trials showed reduction in DVT or pulmonary embolism, a benefit that is also supported by meta-analyses (390, 391). Thus, the evidence strongly supports the value of VTE prophylaxis (grade 1A). The prevalence of infection/sepsis was 17% in those studies in which this could be ascertained. One study investigated only ICU patients only, and 52% of those enrolled had infection/sepsis. The need to extrapolate from general, acutely ill patients to critically ill patients to septic patients downgrades the evidence. That the effect is pronounced and the data are robust somewhat mitigate against the extrapolation, leading to a grade B determination. Because the patient's risk of administration is small, the gravity of not administering may be great, and the cost is low, the strength of the recommendation is strong (1).

Deciding how to provide prophylaxis is decidedly more difficult. The Canadian Critical Care Trials Group compared UFH (5000 IU twice daily) to LMWH (dalteparin, 5000 IU once per day and a second placebo injection to ensure parallel-group equivalence) (392). No statistically significant difference in asymptomatic DVTs was found between the two groups (hazard ratio, 0.92; 95% CI, 0.68−1.23; p = 0.57), but the proportion of patients diagnosed with pulmonary embolism on CT scan, high-probability ventilation perfusion scan, or autopsy was significantly lower in the LMWH group (hazard ratio, 0.51; 95% CI, 0.30−0.88; p = 0.01).The study did not account for the use of other forms of LMWH. These data suggest that LMWH (dalteparin) is the treatment of choice over UFH administered twice daily in critically ill patients. Also, because the study included septic patients, the evidence supporting the use of dalteparin over twice daily UFH in critically ill, and perhaps septic, patients is strong. Similarly, a meta-analysis of acutely ill, general medical patients comparing UFH twice and thrice daily demonstrated that the latter regimen was more effective at preventing VTE, but twice daily dosing produced less bleeding (393). Both critically ill and septic patients were included in these analyses, but their numbers are unclear. Nonetheless, the quality of evidence supporting the use of three times daily, as opposed to twice daily, UFH dosing in preventing VTE in acutely ill medical patients is high (A). However, comparing LMWH to twice daily UFH, or twice daily UFH to three times daily UFH, in sepsis requires extrapolation, downgrading the data. No data exist on direct comparison of LMWH to UFH administered three times daily, nor are there any studies directly comparing twice daily and thrice daily UFH dosing in septic or critically ill patients. Therefore, it is not possible to state that LMWH is superior to three times daily UFH or that three times daily dosing is superior to twice daily administration in sepsis. This downgrades the quality of the evidence and therefore the recommendation.

Douketis et al (394) conducted a study of 120 critically ill patients with acute kidney injury (creatinine clearance

< 30 mL/min) who received VTE prophylaxis with dalteparin 5000 IU daily for between 4 and 14 days and had at least one trough anti-factor Xa level measured. None of the patients had bio-accumulation (trough anti-factor Xa level lower than 0.06 IU/mL). The incidence of major bleeding was somewhat higher than in trials of other agents, but most other studies did not involve critically ill patients, in whom the bleeding risk is higher. Further, bleeding did not correlate with detectable trough levels (394). Therefore, we recommend that dalteparin can be administered to critically ill patients with acute renal failure (A). Data on other LMWHs are lacking. Consequently, these forms should probably be avoided or, if used, anti-factor Xa levels should be monitored (grade 2C). UFH is not renally cleared and is safe (grade 1A).

Mechanical methods (intermittent compression devices and graduated compression stockings) are recommended when anticoagulation is contraindicated (395–397). A meta-analysis of 11 studies, including six RCTs, published in the Cochrane Library concluded that the combination of pharmacologic and mechanical prophylaxis was superior to either modality alone in preventing DVT and was better than compression alone in preventing pulmonary embolism (398). This analysis did not focus on sepsis or critically ill patients but included studies of prophylaxis after orthopedic, pelvic, and cardiac surgery. In addition, the type of pharmacologic prophylaxis varied, including UFH, LMWH, aspirin, and warfarin. Nonetheless, the minimal risk associated with compression devices lead us to recommend combination therapy in most cases. In very-high-risk patients, LMWH is preferred over UFH (392, 399–401). Patients receiving heparin should be monitored for development of heparin-induced thrombocytopenia. These recommendations are consistent with those developed by the American College of Chest Physicians (402).

U. Stress Ulcer Prophylaxis

1. We recommend that stress ulcer prophylaxis using H_2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock who have bleeding risk factors (grade 1B).
2. When stress ulcer prophylaxis is used, we suggest the use of proton pump inhibitors rather than H_2 receptor antagonists (H2RA) (grade 2C).
3. We suggest that patients without risk factors should not receive prophylaxis (grade 2B).

Rationale. Although no study has been performed specifically in patients with severe sepsis, trials confirming the benefit of stress ulcer prophylaxis in reducing upper gastrointestinal (GI) bleeding in general ICU populations included 20% to 25% of patients with sepsis (403–406). This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the risk factors for GI bleeding (eg, coagulopathy, mechanical ventilation for at least 48 hrs, possibly hypotension) are frequently present in patients with severe sepsis and septic shock (407, 408). Patients without these risk factors are unlikely (0.2%; 95% CI, 0.02−0.5) to have clinically important bleeding (407).

Both old and new meta-analyses show prophylaxis-induced reduction in clinically significant upper GI bleeding, which we consider significant even in the absence of proven mortality benefit (409–411). The benefit of prevention of upper GI bleeding must be weighed against the potential (unproven) effect of increased stomach pH on a greater incidence of VAP and *C. difficile* infection (409, 412, 413). (See **Supplemental Digital Content 7 and 8** [http://links.lww.com/CCM/A615], Summary of Evidence Tables for effects of treatments on specific outcomes.) In an exploratory hypothesis, we considered (as did the authors of the meta-analysis) (411) the possibility of less benefit and more harm in prophylaxis among patients receiving enteral nutrition but decided to provide one recommendation while lowering the quality of evidence. The balance of benefits and risks may thus depend on the individual patient's characteristics as well as on the local epidemiology of VAP and *C. difficile* infections. The rationale for considering only suppression of acid production (and not sucralfate) is based on the study of 1,200 patients by Cook et al comparing H_2 blockers and sucralfate (414). More recent meta-analyses provide low-quality evidence suggesting more effective GI bleeding protection with the use of proton pump inhibitors than with H2RA (415–417). Patients should be periodically evaluated for the continued need for prophylaxis.

V. Nutrition

1. We suggest administering oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hrs after a diagnosis of severe sepsis/septic shock (grade 2C).
2. We suggest avoiding mandatory full caloric feeding in the first week, but rather suggest low-dose feeding (eg, up to 500 kcal per day), advancing only as tolerated (grade 2B).
3. We suggest using intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (grade 2B).
4. We suggest using nutrition with no specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

Rationale. Early enteral nutrition has theoretical advantages in the integrity of gut mucosa and prevention of bacterial translocation and organ dysfunction, but also concerning is the risk of ischemia, mainly in hemodynamically unstable patients.

Unfortunately, no clinical trial has specifically addressed early feeding in septic patients. Studies on different subpopulations of critically ill patients, mostly surgical patients, are not consistent, with great variability in the intervention and control groups; all are of low methodological quality (418–427) and none was individually powered for mortality, with very low mortality rates (418–420, 423, 426). Authors of previously published meta-analyses of optimal nutrition strategies for the critically ill all reported that the studies they included had high heterogeneity and low quality(418–430). Although no consistent effect on mortality was observed, there was evidence of benefit from some early enteral feeding on secondary outcomes,

such as reduced incidence of infectious complications (418, 422, 426, 427–430), reduced length of mechanical ventilation (421, 427), and reduced ICU (421, 427) and hospital stays (428). No evidence of harm was demonstrated in any of those studies. Therefore, there is insufficient evidence to issue a strong recommendation, but the suggestion of benefit and absence of harm supports a suggestion that some enteral feeding is warranted.

Studies comparing full caloric early enteral feeding to lower targets in the critically ill have produced inconclusive results. In four studies, no effect on mortality was seen (431–434); one reported fewer infectious complications (431), and the others reported increased diarrhea and gastric residuals (433, 434) and increased incidence of infectious complications with full caloric feeding (432). In another study, mortality was greater with higher feeding, but differences in feeding strategies were modest and the sample size was small (435). Therefore, evidence is insufficient to support an early target of full caloric intake and, indeed, some possibility of harm exists. Underfeeding (60%−70% of target) or trophic feeding (upper limit of 500 kcal) is probably a better nutritional strategy in the first week of severe sepsis/septic shock. This upper limit for trophic feeding is a somewhat arbitrary number, but based in part on the fact that the two recent studies used a range of 240−480 kcal (433, 434). Underfeeding/trophic feeding strategies did not exclude advancing diet as tolerated in those who improved quickly.

Some form of parenteral nutrition has been compared to alternative feeding strategies (eg, fasting or enteral nutrition) in well over 50 studies, although only one exclusively studied sepsis (436), and eight meta-analyses have been published (429, 437–443). Two of the meta-analyses summarize comparisons of parenteral nutrition vs. fasting or intravenous glucose (437, 438), and six look at parenteral vs. enteral nutrition (429, 439–443), two of which attempted to explore the effect of early enteral nutrition (441, 442). Recently, a study much larger than most earlier nutrition trials compared ICU patients randomized to early use of parenteral nutrition to augment enteral feeding vs. enteral feeding with only late initiation of parenteral nutrition if necessary (444).

No direct evidence supports the benefits or harm of parenteral nutrition in the first 48 hrs in sepsis. Rather, the evidence is generated predominantly from surgical, burn, and trauma patients. None of the meta-analyses reports a mortality benefit with parenteral nutrition, except one suggesting parenteral nutrition may be better than late introduction of enteral nutrition (442). Several suggested that parenteral nutrition had higher infectious complications compared both to fasting or intravenous glucose and to enteral nutrition (429, 431, 438, 439, 442). Enteral feeding was associated with a higher rate of enteral complications (eg, diarrhea) than parenteral nutrition (438). The use of parenteral nutrition to supplement enteral feeding was also analyzed by Dhaliwal et al (440), who also reported no benefit. The trial by Casaer et al (444) reported that early initiation of parenteral nutrition led to longer hospital and ICU stays, longer duration of organ support, and higher incidence of ICU-acquired infection. One-fifth of patients had sepsis and there was no evidence of heterogeneity in treatment effects across subgroups, including the sepsis subjects. Therefore, no studies suggest the superiority of TPN over enteral alone in the first 24 hrs. In fact, there is a suggestion that enteral nutrition may in fact be superior to TPN vis-à-vis infectious complications and possibly requirement for intensive care and organ support.

Immune system function can be modified through alterations in the supply of certain nutrients, such as arginine, glutamine, or omega-3 fatty acids. Numerous studies have assessed whether use of these agents as nutritional supplements can affect the course of critical illness, but few specifically addressed their early use in sepsis. Four meta-analyses evaluated immune-enhancing nutrition and found no difference in mortality, neither in surgical nor medical patients (445–448). However, they analyzed all studies together, regardless of the immunocomponent used, which could have compromised their conclusions. Other individual studies analyzed diets with a mix of arginine, glutamine, antioxidants, and/or omega-3 with negative results (449, 450) including a small study in septic patients showing a nonsignificant increase in ICU mortality (451, 452).

Arginine.

Arginine availability is reduced in sepsis, which can lead to reduced nitric oxide synthesis, loss of microcirculatory regulation, and enhanced production of superoxide and peroxynitrite. However, arginine supplementation could lead to unwanted vasodilation and hypotension (452, 453). Human trials of L-arginine supplementation have generally been small and reported variable effects on mortality (454–457). The only study in septic patients showed improved survival, but had limitations in study design (455). Other studies suggested no benefit (449, 454, 455) or possible harm (455) in the subgroup of septic patients. Some authors found improvement in secondary outcomes in septic patients, such as reduced infectious complications (454, 455) and length of hospital stay (454), but the relevance of these findings in the face of potential harm is unclear.

Glutamine.

Glutamine levels are also reduced during critical illness. Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation. Other potential benefits are enhanced immune cell function, decreased pro-inflammatory cytokine production, and higher levels of glutathione and antioxidative capacity (452, 453). However, the clinical significance of these findings is not clearly established.

Although a previous meta-analysis showed mortality reduction (428), four other meta-analyses did not (458–462). Other small studies not included in those meta-analyses had similar results (463, 464). Three recent well-designed studies also failed to show a mortality benefit in the primary analyses (227, 465, 466), but again, none focused specifically on septic patients. Two small studies on septic patients showed no benefit in mortality rates (467, 468) but a significant reduction in infectious complications (467) and a faster recovery of organ dysfunction (468). Some previous individual studies and meta-analyses

showed positive secondary outcomes, such as reduction in infectious morbidity (461, 462, 465) and organ dysfunction (462). Beneficial effects were found mostly in trials using parenteral rather than enteral glutamine. However, recent and well-sized studies could not demonstrate a reduction of infectious complications (227) or organ dysfunction (465, 466), even with parenteral glutamine. An ongoing trial (REDOXS) of 1,200 patients will test both enteral and parenteral glutamine and antioxidant supplementation in critically ill, mechanically ventilated patients (469). Although no clear benefit could be demonstrated in clinical trials with supplemental glutamine, there is no sign of harm.

The omega-3 fatty acids eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) are eicosanoid precursors. The prostaglandins, leukotrienes, and thromboxanes produced from EPA/GLA are less potent than their arachidonic acid-derived equivalents, reducing the pro-inflammatory impact on the immune response (452, 453). Three early studies were summarized in a meta-analysis that reported a significant mortality reduction, increased ventilator-free days, and reduced risk of new organ dysfunction (470). However, only one study was in septic patients (471), none was individually powered for mortality (472, 473), and all three used a diet with high omega-6 lipid content in the control group, which is not the usual standard of care in the critically ill. The authors who first reported reduced mortality in sepsis (471) conducted a follow-up multicenter study and again found improvement in nonmortality outcomes, though notably with no demonstrable effect on mortality (474). Other studies using enteral (475–477) or parenteral (478–480) fish oil failed to confirm these findings in general critical illness or acute lung injury. Thus, no large, reproducible findings suggest a clear benefit in the use of immunomodulating nutritional supplements in sepsis, though larger trials are ongoing.

W. Setting Goals of Care

1. We recommend that goals of care and prognosis be discussed with patients and families (grade 1B).
2. We recommend that the goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (grade 1B).
3. We suggest that goals of care be addressed as early as feasible, but no later than within 72 hrs of ICU admission (grade 2C).

Rationale. The majority of ICU patients receive full support with aggressive, life-sustaining treatments. Many patients with multiple organ system failure or severe neurologic injuries will not survive or will have a poor quality of life. Decisions to provide less-aggressive life-sustaining treatments or to withdraw life-sustaining treatments in these patients may be in the patient's best interest and may be what patients and their families desire (481). Physicians have different end-of-life practices based on their region of practice, culture, and religion (482). Although the outcome of intensive care treatment in critically ill patients may be difficult to prognosticate accurately, establishing realistic treatment goals is important in promoting patient-centered care in the ICU (483). Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care along with the prognosis into treatment plans (484). Additionally, discussing the prognosis for achieving the goals of care and level of certainty of prognosis has been identified as an important component of surrogate decision-making in the ICU (485, 486). However, variations exist in the use of advanced care planning and integration of palliative and end-of-life care in the ICU, which can lead to conflicts that may threaten overall quality of care (487, 488). The use of proactive family care conferences to identify advanced directives and treatment goals within 72 hrs of ICU admission promotes communication and understanding between the patient's family and the care team; improves family satisfaction; decreases stress, anxiety, and depression in surviving relatives; facilitates end-of-life decision making; and shortens length of stay for patients who die in the ICU (489–494). Clinical practice guidelines for support of the ICU patient and family promote: early and repeated care conferencing to reduce family stress and improve consistency in communication; open flexible visitation; family presence during clinical rounds and resuscitation; and attention to cultural and spiritual support (495). Additionally, the integration of advanced care planning and palliative care focused on pain management, symptom control, and family support has been shown to improve symptom management and patient comfort, and to improve family communication (484, 490, 496).

PEDIATRIC CONSIDERATIONS IN SEVERE SEPSIS (TABLE 9)

While sepsis in children is a major cause of death in industrialized countries with state-of-the-art ICUs, the overall mortality from severe sepsis is much lower than that in adults, estimated at about 2% to 10% (497–499). The hospital mortality rate for severe sepsis is 2% in previously healthy children and 8% in chronically ill children in the United States (497). Definitions of sepsis, severe sepsis, septic shock, and multiple organ dysfunction/failure syndromes are similar to adult definitions but depend on age-specific heart rate, respiratory rate, and white blood cell count cutoff values (500, 501). This document provides recommendations only for term newborns and children in the industrialized resource-rich setting with full access to mechanical ventilation ICUs.

A. Initial Resuscitation

1. We suggest starting with oxygen administered by face mask or, if needed and available, high-flow nasal cannula oxygen or nasopharyngeal continuous positive airway pressure (CPAP) for respiratory distress and hypoxemia. Peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required, then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation (grade 2C).

Rationale. Due to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation; however, during intubation and mechanical ventilation,

TABLE 9. Recommendations: Special Considerations in Pediatrics

A. Initial Resuscitation

1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseus access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation (grade 2C).
2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 secs, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 $mL \cdot kg^{-1} \cdot hr^{-1}$, and normal mental status. $Scvo_2$ saturation ≥70% and cardiac index between 3.3 and 6.0 $L/min/m^2$ should be targeted thereafter (grade 2C).
3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock (grade 1C).
4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock (grade 1C).

B. Antibiotics and Source Control

1. Empiric antibiotics be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (eg H1N1, MRSA, chloroquine resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia) (grade 1D).
2. Clindamycin and anti-toxin therapies for toxic shock syndromes with refractory hypotension (grade 2D).
3. Early and aggressive source control (grade 1D).
4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease (grade 1A).

C. Fluid Resuscitation

1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5–10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In non-hypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises) blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).

D. Inotropes/Vasopressors/Vasodilators

1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation (grade 2C).
2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilator therapies in addition to inotropes (grade 2C).

E. Extracorporeal Membrane Oxygenation (ECMO)

1. Consider ECMO for refractory pediatric septic shock and respiratory failure (grade 2C).

F. Corticosteroids

1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency (grade 1A).

G. Protein C and Activated Protein Concentrate

No recommendation as no longer available.

H. Blood Products and Plasma Therapies

1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia then a lower target > 7.0 g/dL can be considered reasonable (grade 1B).
2. Similar platelet transfusion targets in children as in adults (grade 2C).
3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura (grade 2C).

I. Mechanical Ventilation.

1 Lung-protective strategies during mechanical ventilation (grade 2C)

(*Continued*)

TABLE 9. (*Continued*) Recommendations: Special Considerations in Pediatrics

J. Sedation/Analgesia/Drug Toxicities
1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis (grade 1D).
2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events (grade 1C).
K. Glycemic Control
1. Control hyperglycemia using a similar target as in adults ≤ 180 mg/dL. Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant (grade 2C).
L. Diuretics and Renal Replacement Therapy
1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 10% total body weight fluid overload (grade 2C).
M. Deep Vein Thrombosis (DVT) Prophylaxis
No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.
N. Stress Ulcer(SU) Prophylaxis
No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis.
O. Nutrition
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

increased intrathoracic pressure can reduce venous return and lead to worsening shock if the patient is not volume loaded. In those who desaturate despite administration of face mask oxygen, high-flow nasal cannula oxygen or nasopharyngeal CPAP can be used to increase functional residual capacity and reduce the work of breathing, allowing for establishment of intravenous or intraosseous access for fluid resuscitation and peripheral inotrope delivery (502, 503). Drugs used for sedation have important side effects in these patients. For example, etomidate is associated with increased mortality in children with meningococcal sepsis because of adrenal suppression effect (504, 505). Because attainment of central access is more difficult in children than adults, reliance on peripheral or intraosseous access can be substituted until and unless central access is available.

2. We suggest that the initial therapeutic endpoints of resuscitation of septic shock be capillary refill of ≤ 2 s, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 mL/kg/hr, and normal mental status. Thereafter, $Scvo_2$ saturation greater than or equal to 70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted (grade 2C).

Rationale. Adult guidelines recommend lactate clearance as well, but children commonly have normal lactate levels with septic shock. Because of the many modalities used to measure $Scvo_2$ and cardiac index, the specific choice is left to the practitioner's discretion (506–512).

3. We recommend following the American College of Critical Care Medicine-Pediatric Advanced Life Support guidelines for the management of septic shock (grade 1C).

Rationale. The recommended guidelines are summarized in **Figure 2** (510–512).

4. We recommend evaluating for and reversing pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock (grade 1C).

Rationale. Endocrine emergencies include hypoadrenalism and hypothyroidism. In select patients, intra-abdominal hypertension may also need to be considered (513–515).

B. Antibiotics and Source Control

1. We recommend that empiric antimicrobials be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible, but this should not delay initiation of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (eg, H1N1, methicillin-resistant *S. aureus*, chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia) (grade 1D).

Rationale. Vascular access and blood drawing is more difficult in newborns and children. Antimicrobials can be given intramuscularly or orally (if tolerated) until intravenous line access is available (516–519).

2. We suggest the use of clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension (grade 2D).

Rationale. Children are more prone to toxic shock than adults because of their lack of circulating antibodies to toxins. Children with severe sepsis and erythroderma and suspected toxic shock should be treated with clindamycin to reduce toxin production. The role of IVIG in toxic shock syndrome

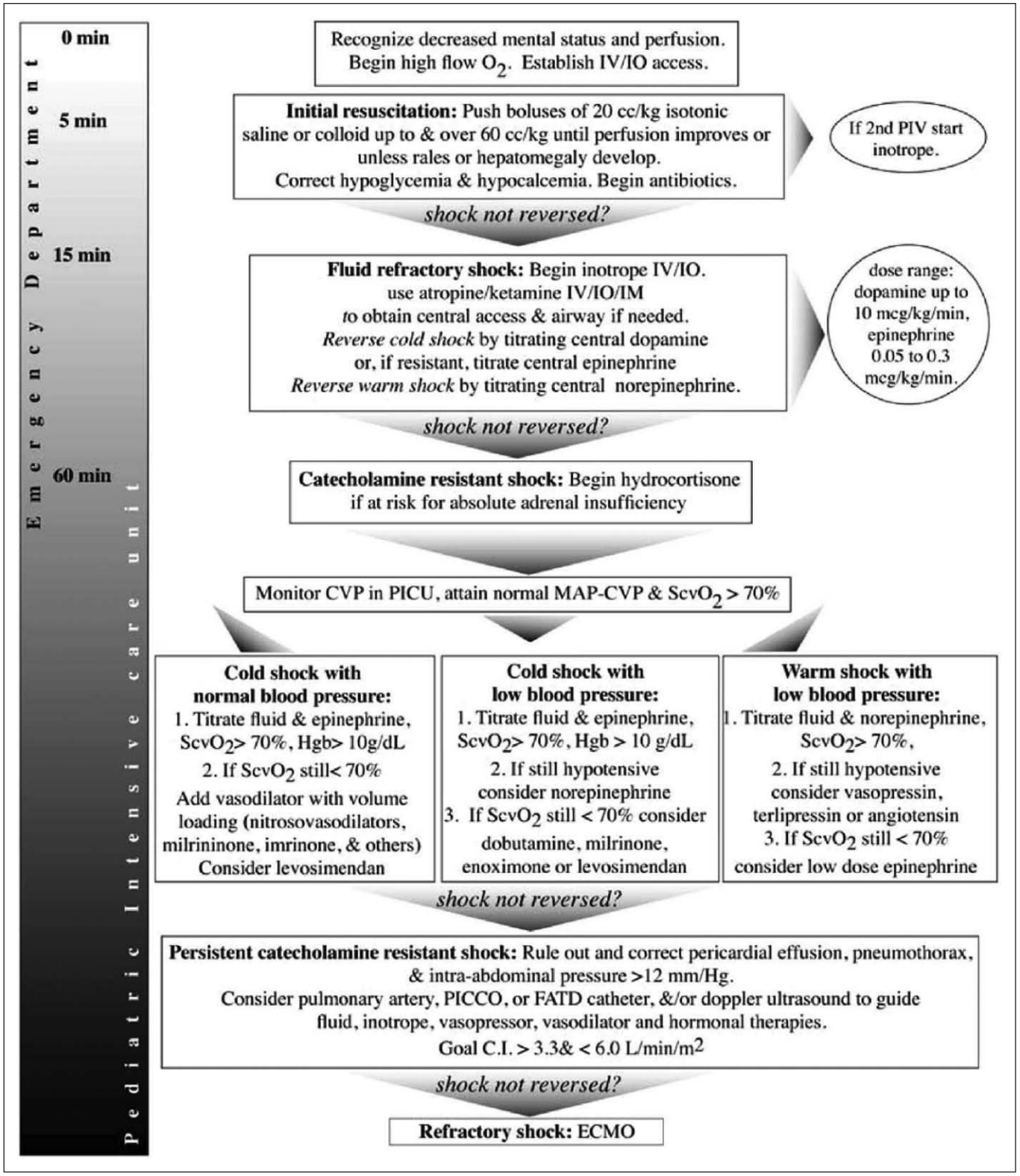

Figure 2. Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support in infants and children. Reproduced from Brierley J, Carcillo J, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666–688.

is unclear, but it may be considered in refractory toxic shock syndrome (520–527).

3. We recommend early and aggressive infection source control (grade 1D).

Rationale. Débridement and source control is paramount in severe sepsis and septic shock. Conditions requiring débridement or drainage include necrotizing pneumonia, necrotizing fasciitis, gangrenous myonecrosis, empyema, and abscesses. Perforated

viscus requires repair and peritoneal washout. Delay in use of an appropriate antibiotic, inadequate source control, and failure to remove infected devices are associated with increased mortality in a synergistic manner (528–538).

4. *C. difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease (grade 1A).

Rationale. In adults, metronidazole is a first choice; however, response to treatment with *C. difficile* can be best with enteral vancomycin. In very severe cases where diverting ileostomy or colectomy is performed, parenteral treatment should be considered until clinical improvement is ascertained (539–541).

C. Fluid Resuscitation

1. In the industrialized world with access to inotropes and mechanical ventilation, we suggest that initial resuscitation of hypovolemic shock begin with infusion of isotonic crystalloids or albumin, with boluses of up to 20 mL/kg for crystalloids (or albumin equivalent) over 5 to 10 mins. These should be titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales develop, inotropic support should be implemented, not fluid resuscitation. In children with severe hemolytic anemia (severe malaria or sickle cell crises) who are not hypotensive, blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).

Rationale. Three RCTs compared the use of colloid to crystalloid resuscitation in children with hypovolemic dengue shock with near 100% survival in all treatment arms (542–544). In the industrialized world, two before-and-after studies observed 10-fold reductions in mortality when children with purpura/meningococcal septic shock were treated with fluid boluses, inotropes, and mechanical ventilation in the community emergency department (545, 546). In one randomized trial, septic shock mortality was reduced (40% to 12%) when increased fluid boluses, blood, and inotropes were given to attain a $Scvo_2$ monitoring goal of greater than 70% (511). A quality improvement study achieved a reduction in severe sepsis mortality (from 4.0% to 2.4%) with the delivery of fluid boluses and antibiotics in the first hour in a pediatric emergency department to reverse clinical signs of shock (547).

Children normally have a lower blood pressure than adults, and a fall in blood pressure can be prevented by vasoconstriction and increasing heart rate. Therefore, blood pressure alone is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Thus, fluid resuscitation is recommended for both normotensive and hypotensive children in hypovolemic shock (542–554). Because hepatomegaly and/or rales occur in children who are fluid overloaded, these findings can be helpful signs of hypervolemia. In the absence of these signs, large fluid deficits can exist, and initial volume resuscitation can require 40 to 60 mL/kg or more; however, if these signs are present, then fluid administration should be ceased and diuretics should be given. Inotrope infusions and mechanical ventilation are commonly required for children with fluid-refractory shock.

D. Inotropes/Vasopressors/Vasodilators

1. We suggest beginning peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation (grade 2C).

Rationale. Cohort studies show that delay in the use of inotropic therapies is associated with major increases in mortality risk (553, 554). This delay is often related to difficulty in attaining central access. In the initial resuscitation phase, inotrope/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 (555). A child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the hemodynamic state (555). Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion. In the case of extremely low systemic vascular resistance despite the use of norepinephrine, the use of vasopressin and terlipressin has been described in a number of case reports, yet evidence to support this in pediatric sepsis, as well as safety data, are still lacking. Indeed, two RCTs showed no benefit in outcome with use of vasopressin or terlipressin in children (556–559). Interestingly, while vasopressin levels are reduced in adults with septic shock, such levels seem to vary extensively in children. When vasopressors are used for refractory hypotension, the addition of inotropes is commonly needed to maintain adequate cardiac output (510, 511, 555).

2. We suggest that patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure be given vasodilator therapies in addition to inotropes (grade 2C).

Rationale. The choice of vasoactive agent is initially determined by the clinical examination; however, for the child with invasive monitoring in place and demonstration of a persistent low cardiac output state with high systemic vascular resistance and normal blood pressure despite fluid resuscitation and inotropic support, vasodilator therapy can reverse shock. Type III phosphodiesterase inhibitors (amrinone, milrinone, enoximone) and the calcium sensitizer levosimendan can be helpful because they overcome receptor desensitization. Other important vasodilators include nitrosovasodilators, prostacyclin, and fenoldopam. In two RCTs, pentoxifylline reduced mortality from severe sepsis in newborns (510, 560–569).

E. Extracorporeal Membrane Oxygenation

1. We suggest ECMO in children with refractory septic shock or with refractory respiratory failure associated with sepsis (grade 2C).

Rationale. ECMO may be used to support children and neonates with septic shock or sepsis-associated respiratory failure (570, 571). The survival of septic patients supported with ECMO is 73% for newborns and 39% for older children, and is highest in those receiving venovenous ECMO (572). Forty-one percent of children with a diagnosis of sepsis requiring ECMO for respiratory failure survive to hospital discharge (573). Venoarterial ECMO is useful in children with refractory septic shock (574), with one center reporting 74% survival to hospital discharge using central cannulation via sternotomy (575). ECMO has been used successfully in critically ill H1N1 pediatric patients with refractory respiratory failure (576, 577).

F. Corticosteroids

1. We suggest timely hydrocortisone therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classic) adrenal insufficiency (grade 1A).

Rationale. Approximately 25% of children with septic shock have absolute adrenal insufficiency. Patients at risk for absolute adrenal insufficiency include children with severe septic shock and purpura, those who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. Initial treatment is hydrocortisone infusion given at stress doses (50 mg/m^2/24 hr); however, infusions up to 50 mg/kg/d may be required to reverse shock in the short-term. Death from absolute adrenal insufficiency and septic shock occurs within 8 hrs of presentation. Obtaining a serum cortisol level at the time empiric hydrocortisone is administered may be helpful (578–583).

G. Protein C and Activated Protein Concentrate

See section, History of Recommendations Regarding Use of Recombinant Activated Protein C.

H. Blood Products and Plasma Therapies

1. We suggest similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (< 70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, then a lower target > 7.0 g/dL can be considered reasonable (grade 1B).

Rationale. The optimal hemoglobin for a critically ill child with severe sepsis is not known. A recent multicenter trial reported no difference in mortality in hemodynamically 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; however, the severe sepsis subgroup had an increase in nosocomial sepsis and lacked clear evidence of equivalence in outcomes with the restrictive strategy (584, 585). Blood transfusion is recommended by the World Health Organization for severe anemia, hemoglobin value < 5 g/dL, and acidosis. An RCT of early goal-directed therapy for pediatric septic shock using the threshold hemoglobin of 10 g/dL for patients with a $Svco_2$ saturation less than 70% in the first 72 hrs of pediatric ICU admission showed improved survival in the multimodal intervention arm (511).

2. We suggest similar platelet transfusion targets in children as in adults (grade 2C).
3. We suggest the use of plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura (grade 2C).

Rationale. We give plasma to reverse thrombotic microangiopathies in children with thrombocytopenia-associated multiple organ failure and progressive purpura because fresh frozen plasma contains protein C, antithrombin III, and other anticoagulant proteins. Rapid resuscitation of shock reverses most disseminated intravascular coagulation; however, purpura progresses in some children in part due to critical consumption of antithrombotic proteins (eg, protein C, antithrombin III, ADAMTS 13). Plasma is infused with the goal of correcting prolonged prothrombin/partial thromboplastin times and halting purpura. Large volumes of plasma require concomitant use of diuretics, continuous renal replacement therapy, or plasma exchange to prevent greater than 10% fluid overload (586–611).

I. Mechanical Ventilation

1. We suggest providing lung-protective strategies during mechanical ventilation (grade 2C).

Rationale. Some patients with ARDS will require increased PEEP to attain functional residual capacity and maintain oxygenation, and peak pressures above 30 to 35 cm H_2O to attain effective tidal volumes of 6 to 8 mL/kg with adequate CO_2 removal. In these patients, physicians generally transition from conventional pressure control ventilation to pressure release ventilation (airway pressure release ventilation) or to high-frequency oscillatory ventilation. These modes maintain oxygenation with higher mean airway pressures using an "open" lung ventilation strategy. To be effective, these modes can require a mean airway pressure 5 cm H_2O higher than that used with conventional ventilation. This can reduce venous return leading to greater need for fluid resuscitation and vasopressor requirements (612–616).

J. Sedation/Analgesia/Drug Toxicities

1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis (grade 1D).

Rationale. Although there are no data supporting any particular drugs or regimens, propofol should not be used for long-term sedation in children younger than 3 years because of the reported association with fatal metabolic acidosis. The use of etomidate and/or dexmedetomidine during septic shock should be discouraged, or at least considered carefully, because these drugs inhibit the adrenal axis and the sympathetic nervous system, respectively, both of which are needed for hemodynamic stability (617–620).

2. We recommend monitoring drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events (grade 1C).

Rationale. Children with severe sepsis have reduced drug metabolism (621).

K. Glycemic Control

1. We suggest controlling hyperglycemia using a similar target as in adults (≤ 180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children (grade 2C).

Rationale. In general, infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4 to 6 mg/kg/min or maintenance fluid intake with dextrose 10% normal saline containing solution is advised (6–8 mg/kg/min in newborns). Associations have been reported between hyperglycemia and an increased risk of death and longer length of stay. A retrospective pediatric ICU study reported associations of hyperglycemia, hypoglycemia, and glucose variability with increased length of stay and mortality rates. An RCT of strict glycemic control compared to moderate control using insulin in a pediatric ICU population found a reduction in mortality with an increase in hypoglycemia. Insulin therapy should only be conducted with frequent glucose monitoring in view of the risks for hypoglycemia which can be greater in newborns and children due to a) relative lack of glycogen stores and muscle mass for gluconeogenesis, and b) the heterogeneity of the population with some excreting no endogenous insulin and others demonstrating high insulin levels and insulin resistance (622–628).

L. Diuretics and Renal Replacement Therapy

1. We suggest the use of diuretics to reverse fluid overload when shock has resolved and if unsuccessful, then continuous venovenous hemofiltration or intermittent dialysis to prevent greater than 10% total body weight fluid overload (grade 2C).

Rationale. A retrospective study of children with meningococcemia showed an associated mortality risk when children received too little or too much fluid resuscitation (549, 553). A retrospective study of 113 critically ill children with multiple organ dysfunction syndrome reported that patients with less fluid overload before continuous venovenous hemofiltration had better survival (629–631),

M. DVT Prophylaxis

1. We make no graded recommendations on the use of DVT prophylaxis in prepubertal children with severe sepsis.

Rationale. Most DVTs in young children are associated with central venous catheters. Heparin-bonded catheters may decrease the risk of catheter-associated DVT. No data exist on the efficacy of UFH or LMWH prophylaxis to prevent catheter-related DVT in children in the ICU (632, 633).

N. Stress Ulcer Prophylaxis

1. We make no graded recommendations on stress ulcer prophylaxis.

Rationale. Studies have shown that clinically important GI bleeding in children occurs at rates similar to those of adults. Stress ulcer prophylaxis is commonly used in children who are mechanically ventilated, usually with H_2 blockers or proton pump inhibitors, although its effect is not known (634, 635).

O. Nutrition

1. Enteral nutrition should be used in children who can tolerate it, parenteral feeding in those who cannot (grade 2C).

Rationale. Dextrose 10% (always with sodium-containing solution in children) at maintenance rate provides the glucose delivery requirements for newborns and children (636). Patients with sepsis have increased glucose delivery needs which can be met by this regimen. Specific measurement of caloric requirements are thought to be best attained using a metabolic cart as they are generally less in the critically ill child than in the healthy child.

SUMMARY AND FUTURE DIRECTIONS

Although this document is static, the optimum treatment of severe sepsis and septic shock is a dynamic and evolving process. Additional evidence that has appeared since the publication of the 2008 guidelines allows more certainty with which we make severe sepsis recommendations; however, further programmatic clinical research in sepsis is essential to optimize these evidence-based medicine recommendations.

New interventions will be proven and 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 results published.

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APPENDIX A

2012 Surviving Sepsis Campaign Guidelines Committee

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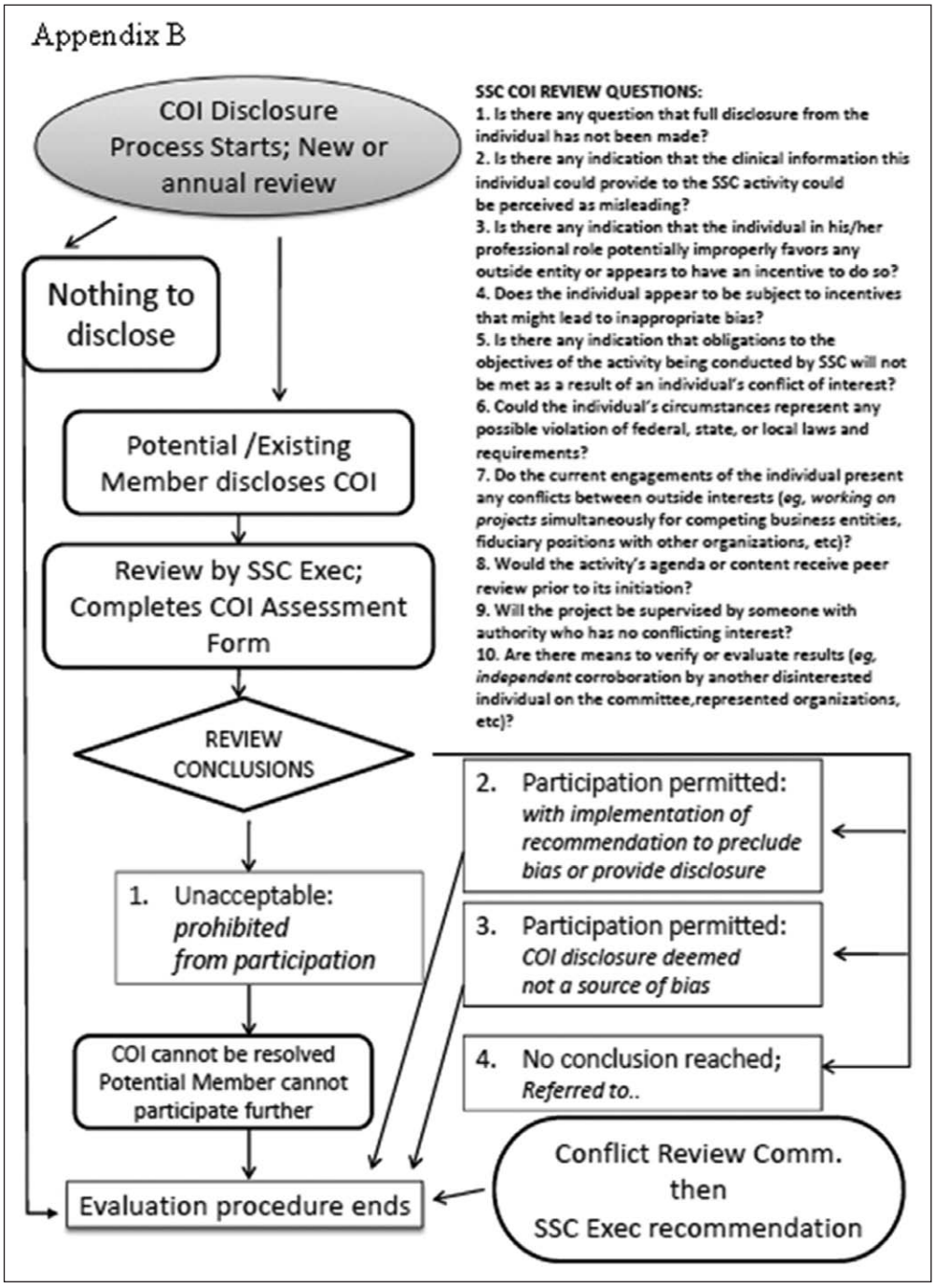
Pediatric Subgroup

Jan A. Hazelzet, Adrienne G. Randolph, Margaret M. Parker, Ann E. Thompson, Paolo Biban, Alan Duncan, Cristina Mangia, Niranjan Kissoon, and Joseph A. Carcillo (Head).

APPENDIX B
Conflict of Interest Process



APPENDIX C
ARDSnet Ventilator Management

Assist control mode—volume ventilation													
Reduce tidal volume to 6 mL/kg lean body weight													
Keep plateau pressure < 30 cm H_2O													
–Reduce tidal volume as low as 4 mL/kg predicted body weight to limit plateau pressure													
Maintain Sao_2/Spo_2 between 88% and 95%													
Anticipated PEEP settings at various Fio_2 requirements													
Fio_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]														

Sao_2 = arterial oxygen saturation, PEEP = positive end-expiratory pressure, Spo_2 = oxygen saturation on pulse oximetry. Adapted from Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.
N Engl J Med 2000; 342:1301–1308.

APPENDIX D
Summary of Ventilator Procedures in the Higher PEEP Groups of the ALVEOLI Trial

Procedure	Value
Ventilator mode	Volume assist/control
Tidal volume goal	6 mL/kg of predicted body weight
Plateau pressure goal	≤ 30 cm H_2O
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥ 7.30 if possible
Inspiration expiration time	1:1—1:3
Oxygenation goal	
Pao_2	55—80 mm Hg
Spo_2	88%—95%
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP < 8 cm H_2O and Fio_2 < 0.40

Allowable combinations of PEEP and Fio_2[a]

Higher PEEP group (after protocol changed to use higher levels of PEEP)

Fio_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1
PEEP	12	14	14	16	16	18	20	22	22	22–24

Note: Complete ventilator procedures and eligibility criteria can be found at www.ardsnet.org.
Spo_2 = oxyhemoglobin saturation as measured by pulse oximetry, Fio_2 = fraction of inspired oxygen, PEEP = positive end-expiratory pressure.
[a]In both study groups (lower and higher PEEP), additional increases in PEEP to 34 cm H_2O were allowed but not required after Fio_2 had been increased to 1.0, according to the protocol.
Adapted from Brower RG, Lanken PN, MacIntyre N, et al: Higher vs. lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.
N Engl J Med. 2004; 351(4):327–336.