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 29 international organizations. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A stand-alone meeting was held for all sub-group 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: We advised the authors to follow the priniciples 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., and the potential drawbacks of making strong recommendations in the presence of low quality evidence were emphasized strong (1) or weak (2). Recommendations are in 3 groups: 1) those directly targeting severe sepsis; 2) recommendations targeting general care of the critically ill patient that are considered high priority in severe sepsis; and 3) pediatric considerations. A formal conflict of interest policy (COI) was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding.*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 before antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 hr of diagnosis of

septic shock (1B) and severe sepsis without septic shock (1C); reassessment of antimicrobial therapy daily for de-escalation, when appropriate (1B); 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 (1A) with consideration of the addition of albumin in patients who continue to require boluses of crystalloid to maintain adequate mean arterial pressure (2B) and the avoidance of hetastarch formulations (1B); initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with 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 there is hemodynamic improvement based on either dynamic or static variables (UG); norepinephrine as the first choice vasopressor to maintain MAP ≥ 65 mm HG (1B); epinephrine when an additional agent is needed to maintain adequate blood pressure (1B); vasopressin 0.03 units/min can be added to high dose norepinephrine to either raise MAP to target or to decrease NE dose but should not be used as the initial vasopressor (UG); dopamine is not recommended except in highly selected fcircumstances (2C); dobutamine infusion 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 mean arterial pressure (1C); not using intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (2C); target a hemoglobin of 7-9 g/dLin the absence of tissue hypoperfusion, ischemic coronary artery disease, or acute hemorrhage(1B); a low tidal volume (1A) and limitation of inspiratory plateau pressure strategy (1B) for acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure (PEEP) in acute lung injury (1B); higher rather than lower level of PEEP for patients with sepsis-induced 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 PaO2/FiO2 ratio <100 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); avoiding neuromuscular blockers if possible in the septic patient *without* ARDS (1C); a short course of neuromuscular blocker of not greater than 48 hrs for patients *with* early, severe ARDS (2C); a protocolized approach to blood glucose management commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL, targeting an upper blood glucose <180 mg/dL (1A); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1B); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding (1B); 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 (2C); and addressing goals of care, including treatment plans and end-of-life planning (as appropriate) (1B), as early as feasible, but no later than within 72 hrs of ICU admission (2C). Recommendations specific to pediatric severe sepsis include: in the presence of respiratory distress and/or hypoxemia, beginning therapy with face mask oxygen, high flow nasal cannula oxygen or nasopharyngeal continuous PEEP (2C), greater use of physical examination therapeutic end points 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 5-10 minutes (2C); more common use of inotropes and vasodilators for low cardiac output septic shock associated with elevated systemic vascular resistance (2C); use of hydrocortisone only in children with suspected or proven “absolute”’ adrenal insufficiency (2C); and more common use of ECMO for refractory respiratory failure associated with septic shock (2C).

Conclusions: Strong agreement existed among a large cohort of international experts regarding many level 1 recommendations for the best current care of patients with severe sepsis. Although a significant number of aspects of care have relatively weak evidence, 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.

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

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Introduction

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 1 in 4 (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 intensive care unit (ICU) and non-ICU settings. In fact, the committee believes that currently the greatest outcome improvement can be made through education and process change for those caring for severe sepsis patients in the non-ICU setting and across the spectrum of acute care. It should also be noted that resource limitations in some institutions and countries may prevent physicians from accomplishing

particular recommendations. These recommendations are intended to be best practice (what the committee considers 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, there is a distinction 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 <70 mm Hg or a SBP decrease >40 mm Hg or < 2 SD below normal for age in the absence of other causes of hypotension. An example of a therapeutic target or typical threshold for the reversal of hypotension is seen in the sepsis bundles for the use of vaspopressors. In the bundles, the *threshold* for mean arterial pressure is ≥65 mm Hg. The different use of *definition* versus *threshold* will be evident throughout this manuscript. 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 - The current clinical practice guidelines are a revision of the 2008 SSC guidelines for the management of severe sepsis and septic shock (7). The first SSC guidelines were published in 2004 (8). The 2004 publication incorporated the evidence available through the end of 2003; the 2008 publication considered evidence through the end of 2007. The current publication is based on an updated literature search into 2012.

Selection of Committee Members - 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 based on creating continuity with the previous guidelines committee membership and content needs for the development process. Four evidence-based medicine experts were selected by the GRADE group.
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).

Under the guidance of the evidence-based medicine experts, 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 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 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 general topic area of the subgroup, as well as appropriate key words of the specific question posed. All questions of the previous guidelines publications were searched, as were pertinent new questions generated by general topic-related 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 data base (ie, MEDLINE, EMBASE), and Cochrane Library (both The Cochrane Database of Systematic Reviews [CDSR] and Database of Abstract of Reviews of Effectiveness [(DARE]). Other databases were optional (ACP Journal Club, Evidence- Based Medicine Journal, Cochrane Registry of Controlled Clinical Trials, http://www.controlled-trials.com/isrctn/ or http://www.controlled-trials.com/mrct/.).Available evidence was summarized using a review manager program in the form of summary 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). The grading of the 2012 guidelines recommendations is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, a structured system for rating quality of evidence and grading strength of recommendations in clinical practice (9-11). The SSC Steering Committee and individual authors collaborated with GRADE representatives to apply the GRADE 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 and, based on the preceding, 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 (see Table 3). Examples of indirectness of the evidence include population studied, interventions used, outcomes measured, and how these relate to the question of interest. Observational (nonrandomized) studies begin as low-quality evidence, but the quality level may be upgraded on the basis of a large magnitude of effect. An example of this is the quality of evidence for early administration of antibiotics. References to online 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 the judgment of strong versus weak recommendation are presented in Table 4. The grade of *strong* or *weak* is considered of greater clinical importance than a difference in letter level of quality of evidence. The committee assessed whether the desirable effects of adherence will outweigh the undesirable effects, and the strength of a recommendation reflects the group's degree of confidence in

that assessment. 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; less 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 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 patient 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 for administering antibiotics within 1 hr of the diagnosis of severe sepsis as well as the recommendation for achieving a CVP of 8 mm Hg and an ScvO2 of 70% in the first 6 hours of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet standards of care as verified by current practice data (see those respective sections of the guidelines for additional information).

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 presented for general discussion among subgroup heads, Surviving Sepsis Campaign (SSC) steering committee (2 co-chairs, 2 co-vice chairs, and an at-large committee member), and several selected key committee members 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 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 for their respective group assignment and then by the entire committee.

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Conflict of Interest Policy

Since the inception of the SSC guidelines in 2004, no members of the committee were from 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 any honoraria for any role in the 2004, 2008, or 2012 guidelines process.

Appendix B shows a flowchart of the COI disclosure process. Committee members who were judged to have either financial or non-financial/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 A detailed description of the disclosure process and all author disclosures appear in online Appendix A in the online supplemental materials to this document. On initial review, 68 financial conflict of interest (COI) disclosures and 54 non-financial disclosures were submitted by committee members. Declared COIs from 19 membersmembers were determined by the COI subcommittee to be not relevant to the guidelines content process. Nine who were determined to

have COI (financial and non-financial) 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 COI that could not be resolved solely by reassignment. One of these individuals was asked to step down from the committee. The other 8 people were assigned to the groups in which they had the least COI. They were required to work within their group with full disclosure as to their conflict of interest when a topic for which they had relevant COI was discussed and 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 one part of a treatment protocol (grade 1C):

(a) Central venous pressure 8–12 mm Hg

(b) Mean arterial pressure (MAP) ≥65 mm Hg

(c) Urine output ≥ 0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$

(d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively.

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

Rationale. Early quantitative resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study (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 8 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 similar patient populations have shown significant mortality reduction compared to historical controls at that institution (See Online Appendix B, Supplemental Bibliography of Quantitative Resuscitation). 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 alluded to above (15). Although as part of performance improvement programs some hospitals have lowered the lactate threshold for triggering quantitative resuscitation in the patient with severe sepsis, these thresholds have not been subjected to randomized trials.

The consensus panel judged use of central venous and mixed venous oxygen saturation 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, in general, 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 six hours of resuscitation, if ScvO2 < 70% or SvO2 equivalent of <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 ≥30% in attempts to achieve the ScvO2 or SvO2 goal are options. The strong recommendation for achieving a CVP of 8 mm Hg and an ScvO2 of 70% in the first 6 hours of resuscitation of sepsis-induced tissue hypoperfusion, although deemed desirable, are not yet standard of care as verified by current practice data. The publication of the initial results of the international SSC performance improvement program demonstrated that adherence to CVP and Scv02 targets for initial resuscitation was low (15).

In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target central venous pressure of 12–15 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 central venous pressures may also be seen with pre-existing 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. Recently published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥65 mm Hg as well as central venous oxygen saturation (ScvO2, measured in superior vena cava, either intermittently or continuously) of ≥70% (18). Many recent 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 mixed venous oxygen saturation (SvO2) runs 5–7% lower than ScvO2 (25). While the committee recognized the controversy surrounding resuscitation targets, an early quantitative resuscitation protocol using CVP and venous blood gasses can be readily established in both ED and ICU settings (26). Recognized limitations to static ventricular filling pressure estimates exist as surrogates for fluid resuscitation (27, 28). However, measurement of central venous pressure 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). Currently 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 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 is high in septic patients with both hypotension and lactate ≥ 4 mmol/L (46.1%) (15). Mortality is also increased in severely septic patients with hypotension alone (36.7%) and lactate ≥ 4 mmol/L alone (30%) (15). If ScvO2 is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. ScvO2 and lactate normalization may also be used as a combined endpoint when both are available. Two recent multi-center randomized trials evaluated a resuscitation strategy that included lactate reduction as a single target or a target combined with ScvO2 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 ScvO2 of 70% or more (37). The intention-to-treat group was 300; however the number of patients actually requiring either ScvO2 normalization or lactate clearance was small (n=30). The second trial included 348 patients with lactate ≥3 mmol/L (36). The strategy in this trial was based on a 20% or more decrease in lactate levels per 2 hours of the first 8 hours in addition to ScvO2 target achievement and was associated with a 9.6% absolute reduction in mortality (P= 0.067; adjusted hazard ratio, .61; 95% confidence interval, 0.43-0.87; P= 0.006).

B. Screening for Sepsis and Performance Improvement

1. We recommend routine screening of 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 diagnose severe sepsis is thought to be a critical component of reducing mortality from sepsis-related multiple organ dysfunction (35). Lack of early recognition of sepsis is a major obstacle to sepsis bundle initiation. Sepsis screening tools have been developed to monitor ICU patients (37-41). Implementation of these sepsis screening tools 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, 43-46). Improvement in the process of 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, dietetics, and administration) and a 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 of indicator compliance and can help identify areas for additional performance 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 areis 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 Surviving Sepsis Campaign 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 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 edition of the guidelines. As a result, for the 2012 version, management bundle was dropped and the resuscitation bundle was broken into 2 parts as shown in Figure 1. Note that target measures are not considered in scoring compliance with the bundles. The targets per the original protocol are included with the bundles for reference purposes (13).

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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 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 hr.) 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 not associated with 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 anti-infective dose, obtaining those cultures before starting 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 >48 hr), 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 through the vascular access device is positive much earlier than the peripheral blood culture (ie, >2 hr earlier), the data support the concept that the vascular access device is the source of the infection (3651, 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). Quantitative (or semi-quantitative) 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 (>5 PMN/high powered field and <10 squamous cells/ low powered field) and if culture of the sample 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 at present for the use of these markers to distinguish between severe infection from other acute inflammatory states (56-58).

In the near future, rapid, non-culture-based diagnostic methods (polymerase chain reaction, mass spectroscopy, microarrays) might be extremely 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 already been administered before culture samples have been obtained. Clinical experience remains limited to date 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 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available, for the early diagnosis of invasive candidiasis.

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 been shown to become positive 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 (grade1C). Sampling of potential sources of infection should occur as they are

identified and in consideration of patient risk for transport and invasive procedures(for example careful coordination and aggressive monitoring if decision is made to transport for a CT guided needle aspiration). Bedside studies, such as ultrasound, may avoid patient transport.

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

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 recent studies (15, 68, 70-72). One study done in emergency department patients showed that if antibiotics were given prior versus after onset of shock outcome was influenced (improved survival) butshowed no incremental benefit on survival based on time of antibiotic administration (73). Overall, data support giving antibiotics as soon as possible in patients with severe sepsis with or without septic shock (15, 68, 70-72, 74-78). Administration of antimicrobial agents with a spectrum of activity likely to treat the responsible pathogen(s) effectively should begin within 1 hr after the diagnosis of severe sepsis and septic shock is made. This should be the target goal when managing patients with septic shock whether they are located within the hospital ward, the

emergency department, or within the intensive care unit. 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 standard of care as verified by current 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 for long 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, in the 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* (ORSA or MRSA), 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(79). 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 *C. 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 immunosupressed 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 , There is ample evidence 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, 80,81). Recent exposure to antimicrobials (within last 6 months) should be considered in choosing 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 antimicrobial agent. Patients with sepsis often have abnormal and often 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 are attained that maximize efficacy and minimize toxicity (82, 83).

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 (1B).

Rationale. Once the causative pathogen has been identified, the most appropriate antimicrobial agent should be chosen that covers the pathogen and is safe and cost effective. 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, etc). Decisions on definitive antibiotic choices need to be made 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 the need to give the patient 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 to date relating to the use of procalcitonin as a tool to discontinue unnecessary antimicrobials (58, 84). However, clinical experience with this strategy is limited and the potential for harm remains a concern (84). No evidence exists to demonstrate this practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic-related diarrhea from *C. difficile*. One recent study failed to show benefit of daily PCT measurement as a guide to early antibiotic therapy or survival benefit (85).

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 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 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 complexcombination 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 regimens containing carbapenems, colistin, rifampin, or other agents. However, a recent controlled trial suggested that adding a fluoroquinolone to a carbapenem did not improve outcome as empiric therapy in a population at low risk for infection with resistant microorganisms (86).

4b. When used empirically in patients with severe sepsis, we suggest that combination therapy should not be administered for >3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 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 warrented.

Rationale. A recent 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 (87-91). In light of the increasing frequency of resistance to antimicrobial agents in many parts of the world, broad spectrum coverage generally requires initial use of combinations of antimicrobial agents. Combination therapy used in this context connotes at least 2 different classes of antibiotics (usually a beta-lactam agent with a macrolide, fluoroquinolone, or aminoglycoside for select patients). A recent controlled trial however suggest 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. 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, multi-drug resistant gram negative pathogens) (92-94), 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 (90, 91, 95, 96). Combination therapy for suspected or known *Pseudomonas aeruginosa* or other multi-resistant gram-negative pathogens, pending susceptibility results, increases the likelihood that at least one drug is effective against that strain and positively affects outcome (89, 97).

5. We suggest that the duration of therapy typically be 7–10 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).

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). Appropriate viral cultures and real-time polymerase chain reaction

(PCR) (more sensitive and specific) should be obtained but should not delay prompt administration of antiviral therapy.

overt sepsis resulting from mixed bacterial/viral infection *Rationale.* Recommendations for antiviral treatment include the use of 1) 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); 2) early antiviral treatment of suspected or confirmed influenza among persons at higher risk for influenza complications; and 3) 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 (98,99). Susceptibility to antivirals is highly variable in a rapidly evolving virus such as influenza and therapeutic decisions need to be guided with updated information regarding the most active, strain-specific, antiviral agents during influenza epidemics (100, 101).

The role of cytomegalovirus (CMV) and other herpes viruses as significant pathogens in septic patients, especially those not known to be severely immunocompromised, remains unclear. Active CMV viremia is quite common (15-35%) in critically ill patients; the presence of CMV in the blood stream has been repeatedly found to be a poor prognostic indicator (102,103). 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 (104). No recommendations on treatment 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 (105).

7. We recommend that antimicrobial agents not be used in patients with severe inflammatory states determined to be of noninfectious cause (grade 1C).

Rationale. When infection is found not to be present. *a*ntimicrobial 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 >50% of cases of severe sepsis or septic shock if they 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 peri-pancreatic 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 on infection amenable to source control measures (specifically the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) (106). 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 (107-109) and removing

intravascular access devices that are potentially the source of severe sepsis or septic shock promptly after establishing other sites for vascular access (110,111).

A randomized, controlled trial comparing early versus delayed surgical intervention for peri-pancreatic necrosis showed better outcomes with a delayed approach (112). Moreover, a recent, 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 (113). However, areas of uncertainty exist, such as definitive documentation of infection and appropriate length of delay. The selection of optimal source control methods must weigh the benefits and risks of the specific intervention as well as risks of transfer (114). Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. Surgical intervention should be considered when lesser interventional approaches are inadequate or when diagnostic uncertainty persists despite radiologic evaluation. Specific clinical situations require consideration of available choices, patient's preferences, and clinician's expertise.

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; this infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. We suggest oral chlorhexidine gluconate (CHG) be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia 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, etc) should be instituted during the care of septic patients as recently reviewed in the nursing considerations for the Surviving Sepsis Campaign (115). The role of selective decontamination of the digestive tract

(SDD) with systemic antimicrobial prophylaxis and its variants (eg, selective oral decontamination [SOD], or oral chlorhexidine gluconate [CHG]) continues to be a contentious issue ever since the concept was first developed more than 30 years ago. The notion of limiting the acquisition of opportunistic, often multi-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 (116). The data indicate an overall reduction in ventilator-associated pneumonia (VAP) but no consistent improvement in mortality, except for selected populations in some studies. Most of the available literature do not specifically address the efficacy of SDD in patients who present with sepsis, but some do (117-119).

Oral CHG is relatively easy to apply, 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 (120-122). The grading is 2B for both SOD and CHG as the group felt the risk was less with CHG and is better accepted despite less published literature than with SOD.

Online Appendix C shows a GRADEpro Summary of Evidence Table regarding the use of topical digestive tract antibiotics and chlorhexidine for prophylaxis against VAP.

Hemodynamic Support and Adjunctive Therapy

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 hydroxy ethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).

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

Rationale. The absence of any clear benefit following the administration of colloid solutions when 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. It also supports a high grade recommendation advising against the routine use of colloid solutions in the initial resuscitation of this patient group.

Three recent multicenter randomized controlled trials evaluating HES 6%130/0.4 solutions (tetra starches) have been published. CRYSTMAS demonstrated no difference in mortality with HES versus 0.9% normal saline (31% versus 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. In a sicker patient cohort, a Scandinavian multicenter study in septic patients (6S Trial Group) showed increased mortality rates with HES 130/0.42 fluid resuscitation compared to Ringer's acetate (51% versus 43%. P=0.03) (123, 124). In a heterogenous population of patients admitted to intensive care the CHEST study (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% versus 17%, P=0.26) . In this trial, the need for renal replacement therapy was higher in the HES group (7.0 versus 5.8%, RR 1.21; 95% CI 1.00-1.45, p=0.04) **(125)**. A meta-analysis of 56 randomized trials found no overall difference in mortality between crystalloids and artificial colloids (modified gelatins, hydroxyethyl starches, dextran) when used for initial fluid resuscitation (126). 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 when compared to other fluids (RR=1.15; > 95% CI: 0.95 to 1.39, random effect; I^2= 0%) (127-129). However, these solutions increased substantially the risk of acute kidney injury (RR=1.60, 95% CI: 1.26 to 2.04; I^2= 0%) (127-129).

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.

The SAFE study indicated that albumin administration was safe and equally as effective as 0.9% saline (130). A recent meta-analysis aggregated data from 17 randomized trials (n=1977) of albumin versus other fluid solutions in patients with severe sepsis/septic shock (131). There were 279 deaths among 961 albumin-treated patients vs 343 deaths among 1016 patients treated with other fluids, thus favoring albumin (OR= 0.82, 95%CI: 0.67 to 1.00; I^2= 0%). When compared to crystalloids (7 trials, n=1441), the OR of dying was significantly reduced for albumin-treated patients, 0.78 (95%CI: 0.62 to 0.99, I^2= 0%). A recent multicenter randomized trial (n=794) in patients with septic shock, compared intravenous albumin (20 g, 20%) every 8 hours for 3 days to intravenous saline solution (131). In this trial, albumin therapy was associated with 2.2% absolute reduction in 28-day mortality (from 26.3 to 24.1%), which did not achieve statistical significance. These data support a low level recommendation regarding the use of albumin in patients with sepsis and septic shock. See GRADEpro Summary of Evidence Table in online supplemental material

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 (132). These tests are based on monitoring changes in stroke volume during mechanical ventilation or after passive leg raising in spontaneously breathing patients. A recent systematic review (29 trials, n=685 critically ill patients) has analyzed 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 (133). The diagnostic OR of fluid responsiveness was 59.86 (14 trials, 95%CI: 23.88–150.05) and 27.34 (5 trials, 95%CI: 3.46–

55.53) for the pulse pressure variation (PPV) and the stroke volume variation (SVV), respectively. Utility of PPV and SVV 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 mean arterial pressure (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 mean arterial pressure, auto-regulation 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 (134,135). The titration of norepinephrine to a MAP as low as 65 mm Hg has been shown to preserve tissue perfusion (135). Note that the consensus definition of sepsis-induced hypotension for use of MAP for the diagnosis of severe sepsis is different (MAP < 70 mm Hg) from the evidence-based medicine 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, and in a young, previously normotensive patient, a lower MAP might be adequate. Supplementing end points, such as blood pressure, with assessment of regional and global perfusion, such as blood lactate concentrations, 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, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary, for instance 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 units/minute can be added to norepinephrine (NE) with the intent of raising MAP to target 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. We suggest dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of arrhythmias and/or low heart rate). (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).

Rationale. An extensive literature contrasts the physiologic effects of vasopressor and combined inotrope/vasopressors selection in septic shock (Table 6) (136-148). Table 6 depicts a GRADEproSummary of Evidence Table comparing dopamine and norepinephrinethe treatment of septic shock. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and lesser 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 (149). It may also influence the endocrine response via the hypothalamic pituitary axis and have immunosuppressive effects. However, information from 5 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 (137,150-153). Indeed, the relative risk of short term mortality was 0.91 (95% CI:0.84 to 1.00;fixed effect; I^2=0%) in

favor of norepinephrine. . A recent meta-analysis showed dopamine was associated with an increased risk. (relative risk 1.10[1.01-1.20], *P*=0.035). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk 2.34[1.46-3.77], *P*=0.001) (154). Although some human and animal studies suggest epinephrine has deleterious effects on splanchnic circulation and produces hyperlactemia, there is no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen 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; 0.77 to 1.21; fixed effect; I^2=0%) (143, 148, 155, 156). Epinephrine may increase aerobic lactate production via stimulation of skeletal muscles' beta-2 adrenergic receptors and thus may prevent the use of lactate clearance to guide resuscitation. With its almost pure alpha-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 (157).. Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (158). Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits (159164). Terlipressin has similar effects but is long acting (165).. Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock the concentration decreases to normal range in the majority of patients between 24 and 48 hrs (166). 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, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 units/min, showed no difference in outcome in the intent to treat population (167). 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 ≥15 µg/min norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where

alternative vasopressors have failed (168). Information from 7 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 (94, 96, 98, 100,160,162,165,167,169-171). Indeed, the relative risk of dying was 1.12 (95%CI: 0.96 to 1.30; fixed effects; I^2=0%). See GRADEpro Summary of Evidence Tables in online supplement. However, the risk of supraventricular arrhythmias was increased with norepinephrine (RR=7.25; 95%CI: 2.30 to 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) (172,173). 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 mean arterial pressure (grade 1C).

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

Rationale. Dobutamine is the first choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure. Septic patients who remain hypotensive after fluid resuscitation may have low, normal, or increased cardiac outputs. Therefore, treatment with a combined inotrope/vasopressor, such as norepinephrine or 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 mean arterial pressure and cardiac output. Large prospective clinical trials that included critically ill ICU patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal targets by use of dobutamine (174,175). 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). In case this is not achievable, we suggest intravenous hydrocortisone 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 for selection of patients for an optional hydrocortisone therapy. One French multicenter, randomized controlled trial (RCT) of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors for more than 60 min) showed a significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as postadrenocorticotropic hormone [ACTH] cortisol increase ≤9 μg/dL) (176). Two additional smaller RCTs also showed significant effects on shock reversal with steroid therapy (177,178). In contrast, a large,

European multicenter trial (CORTICUS) that enrolled patients without sustained shock and having a lower risk of death than in the French trial failed to show a mortality benefit with steroid therapy (179). 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, resulting in baseline (placebo) 28-day mortality of respectively 61% and 31% in the former and latter trial. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. In recent years, there have been several systematic reviews on the use of low-dose hydrocortisone in septic shock with contradictory results: Annane analyzed 12 studies in a meta-analysis and calculated a significant reduction of 28-day mortality by 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 used a similar technique, but only 81). 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 (182), and identified only 6 high-level RCTs as adequate for systematic review (176-170,183,184), thus confirming the lack of evidence that the use of low-dose hydrocortisone improves the patients' outcome (182). When only these 6 studies are analyzed, we found that in "low risk" patients from 3 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 3 studies, who had a placebo mortality of more than 60%, showed a non-significant trend to lower mortality by using hydrocortisone. . See Online Appendix D 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 The observation of a potential interaction between steroid use and ACTH test was not statistically significant (176). Furthermore, there was no evidence of this distinction between responders and nonresponders in a recent multicenter trial (179). 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 (185). 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 (186. 187). Moreover, a sub-analysis of the CORTICUS trial (179) revealed that the use of etomidate before application of low-dose steroids was associated with an increased 28-day mortality (188).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 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 (176,178,179), and in 2 RCTs, therapy was decreased after shock resolution (177,183). In 4 RCTs steroids were tapered over several days (177-179,183), and in 2 RCTs (176,184), steroids were withdrawn abruptly. One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids (189). Moreover, a recent 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 time of hydrocortisone therapy (190).

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. However, whether low-dose steroids have a preventive potency in reducing the incidence of severe sepsis and saptic shock in critically ill patients still cannot be answered. A preliminary study of stress-dose level steroids in community acquired pneumonia showed improved outcome measures in a small population (191), and a recent confirmatory RCT revealed reduced hospital length of stay without

affecting mortality (192). 5. When low-dose hydrocortisone is given, we suggest using continuous infusion rather than repetitive bolus injections (2C).

Rationale: Several randomized trials on the use of low-dose hydrocortisone in septic shock patients revealed a significant increase of hyperglycemia and hypernatremia (176) as side effects. A small prospective study demonstrated that repetitive bolus application of hydrocortisone leads to a significant increase of blood glucose; this peak effect was not detectable during continuous infusion. Furthermore, it was shown that there is a considerable inter-individual variability of this blood glucose peak after the hydrocortisone bolus (193). Although an association of hyperglycemia and hypernatremia with outcome measures of patients could not be shown so far, good practice includes strategies for avoiding and/or detection of these side effects.

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 hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 –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 7–9 g/dL when compared with 10–12 g/dL was not associated with increased mortality in critically ill adults (194). There were no significant differences in 30-day mortality between treatment groups in the subgroup of patients with severe infections and septic shock (22.8 percent and 29.7 percent, respectively; P=0.36),

Although less applicable to septic patients, a randomized trial in patients undergoing cardiac surgery with cardiopulmonary bypass supports a restrictive transfusion strategy using a threshold hematocrit of <24% (hemoglobin approximately 8 g/dL) as equivalent to a transfusion threshold of hematocrit of <30% (hemoglobin approximately 10 g/dL) (195). Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption (196-198). 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 $ScvO_2$ 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 (199, 200). 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 co-existing conditions that meet indications for use of erythropoietin.

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

Rationale. Although clinical studies have not assessed the impact of transfusion of fresh frozen plasma on outcomes in critically ill patients, professional organizations have recommended fresh frozen plasma for coagulopathy when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgical or invasive procedures (201-204). In addition, transfusion of fresh frozen plasma in nonbleeding patients with mild abnormalities of prothrombin time usually fails to correct the prothrombin time (205, 206). There are no studies to suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.

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

Rationale. A Phase III clinical trial of high-dose antithrombin did not demonstrate any beneficial effect on 28-day all cause mortality in adults with severe sepsis and septic shock. High-dose antithrombin was associated with an increased risk of bleeding when administered with heparin (207). Although a *post hoc* subgroup analysis of patients with severe sepsis and high risk of death showed better survival in patients receiving antithrombin, antithrombin cannot be recommended until further clinical trials are performed (208).

5. In patients with severe sepsis, we suggest that platelets be administered prophylactically when counts are $\leq$10,000/mm^3 (10 x 10^9/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are $\leq$ 20,000/mm^3 (20 x 10^9/L) if the patient has a significant risk of bleeding. Higher platelet counts ($\geq$50,000/mm^3 [50 x 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 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 (201, 203,204,209,210). 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 that may be relevant to patients with severe sepsis include fever >38° C, recent minor hemorrhage, rapid decrease in platelet count, and other coagulation abnormalities (204, 209,210).

L. Immunoglobulins

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

Rationale: One larger multi-center RCT (n=624) (211) in adult patients and one large multi-national RCT in infants with neonatal sepsis (n=3493) (212) found no benefit for intravenous immunoglobulin (IVIG). For pediatric considerations based on this trial see Section III. A recent meta-analysis by the Cochrane collaboration (213) which did not include this most recent RCT identified 10 polyclonal intravenous immunoglobulin (IVIG) trials (n=1430) and 7 trials on IgM enriched polyclonal IVIG (n=528). Overall compared to placebo, IVIG resulted in a significant reduction in mortality (RR 0.81, 95% CI 0.70. to 0.93 and 0.66; 95 CI 0.51-0.85, respectively). Also the subgroup of IgM enriched IVIG's (n=7 trials) showed a significant reduction in mortality in comparison to placebo (RR 0.66; 95% CI 0.51 to 0.85). However, trials with low risk of bias showed no reduction in mortality with polyclonal IVIG (RR 0.97; 95 CI 0.81-1.15; 5 trials n=945). Three of these trials (211,214,215) used standard polyclonal IVIG, and two IgM enriched IV (216,217).

These findings are in accordance with 2 older meta-analyses (218, 219) from other Cochrane authors. One systematic review (218) included a total of 21 trials and showed a relative risk of death with immunoglobulin treatment of 0.77 (95% CI 0.68-0.88); however, including only high quality trials with a total of 763 patients showed a relative risk of 1.02 (95% CI 0.84-1.24). Similarly, Laupland et al (219) found a significant reduction in mortality with the use of IVIG treatment OR 0.66 (95% confidence interval 0.53-0.83; $p<0.005$). When only high quality studies were pooled, the OR for mortality was 0.96 (CI 0.71-1.3; $p=0.78$). Two meta-analyses, which used less strict criteria to identify sources of bias or did not discuss their criteria for the assessment of study quality, found significant improvement of patient mortality by IVIG treatment (220,221). Kreymann et al (220), who in contrast to the most recent Cochrane review classified 5 studies that investigated IgM enriched-preparation as high quality studies combinino studies in adult and neonate studies, found an OR for mortality of 0.5 (95% CI 0.34-0.73).

Most studies on IVIG are small studies; some of them have methodological flaws, the only larger study (n=624) showed no effect. There is substantial heterogeneity with subgroup effects between IgGM-

enriched and nonenriched formulations. 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).

Rationale. Selenium was hoped to correct the known reduction of selenium concentration observed in sepsis patients and further provide a pharmacologic effect through antioxidant defense in humans. Although there are some randomized controlled trials available, the evidence on the use of intravenous application of selenium is still very weak. Only one larger clinical trial has examined the impact of selenium supplementation on mortality and reported no significant impact on the intent-to-treat populationwith severe SIRS, sepsis, or septic shock (OR 0.66, 95% CI: 0.39-1.10, p=0.109) (222). Overall, there was a trend toward a concentration-dependent reduction in mortality; no differences in secondary outcomes or adverse events were detected. Finally, there was no comment on standardization of sepsis management in this study, which recruited 249 patients over a time period of 6 years (1999-2004) (222).

A French RCT in a smaller population revealed no effect on primary (shock reversal) or secondary (days on mechanical ventilation, ICU mortality) endpoints (223). A smaller RCT investigating the effect of selenium on the development of VAP 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 (224). This is in accordance with 2 RCTs that resulted in reduced number of infectious episodes (225) or glutathione peroxidase concentrations (227); both studies, however, could not show a beneficial effect on secondary outcome measures (renal replacement, ICU mortality) (225, 226).

A recent large RCT tried to determine if addition of relatively low doses of supplemental selenium (glutamine was also tested in a 2-factorial design) to parenteral nutrition in critically ill patients is able to reduce infections and improve outcome (227). Selenium supplementation did not significantly affect patients developing a new infection (OR 0.81, 95% CI: 0.57-1.15), and 6- month mortality was not different (OR 0.89, 95% CI 0.62-1.29). In addition, length of stay, days of antibiotic use, and modified SOFA score were not significantly affected by selenium (228).

Besides the lack of evidence, the questions of optimal dosing and application mode still 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 (228)); this, however, has not been tested in humans. Altogether, 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 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 (mortality 24.7 % in patients given rhAPC and 30.8% in placebo, p 0.005) (229). The 2004 SSC guidelines recommended use of rhAPC in line with the product labeling instructions required by the US 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 rhAPC ineffective in less severely ill patients with severe sepsis as well as in children (230,231). The 2008 SSC recommendations reflected these findings and the

strength of the rhAPC recommendation for adults was downgraded to a suggestion for use in adult patients with a clinical assessment of high risk of death, most of whom will have APACHE II scores ≥25 or multiple organ failure (grade 2C; quality of evidence was also downgraded from 2004, from B to C) (6). The 2008 guidelines also recommended against use of rhAPC in lower risk adult patients, most of whom will have APACHE II score ≤20 or single organ failures (grade 1A), as well as recommending 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 % in patients given rhAPC and 24.2 % in placebo group) with a relative risk of 1.09 and a p value of 0.31(232). The drug was withdrawn from the market and is no longer available, negating any need for SSC recommendation regarding its use.

SUPPORTIVE THERAPY OF SEVERE SEPSIS

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

1. We recommend that clinicians target a tidal volume of 6 mL/kg rather than 12 ml/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A).

2. We recommend that plateau pressures be measured in patients withARDS 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 Acute Respiratory Distress Syndrome (ARDS) (233). For this document, we have used the updated Berlin definition and used the term ARDS as an inclusive term for the syndromes previously known as ALI and ARDS (234).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 (235-239).. These studies showed differing results that may have been caused by differences between airway

pressures in the treatment and control groups (234(235, 240). Several meta-analyses suggest decreased mortality in patients with a pressure and volume limited strategy for established ARDS (241, 242).

The largest trial of a volume- and pressure limited strategy showed an absolute 9% decrease of all-cause mortality in patients with ALI or 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(234). 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 H2O (243. 244) The validity of this ceiling value will depend on the breathing effort, as patients who are actively inspiring 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(245) as lower plateau pressures were associated with decreased in-hospital mortality (246).

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 1–2 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 H2O. If the plateau pressure remains >30 cm H_2Oafter 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 ICP) 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 (247,248).
A A number of observational trials in mechanically ventilated patients have demonstrated a decreased risk of developing ARDS when smaller trial volumes are used (249-252). Accordingly, high tidal volumes and plateau pressures should be avoided in mechanically ventilated patients at risk for developing ARDS, including patients 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 severe ARDS (grade 2C).
Rationale. Raising PEEP in ALI/ARDS keeps lung units open to participate in gas exchange. This will increase PaO_2 when PEEP is applied through either an endotracheal tube or a face mask (253-255).. 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 versus lower levels of PEEP in conjunction with low tidal volumes did not show benefit or harm (256-258)).A meta-analysis using individual patient data showed no benefit in all patients with ALI; however, patients with ARDS had decreased mortality with the use of higher PEEP, whereas those with ALI but not ARDS did not.(259). 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 (260). The second option is to titrate PEEP based on severity of oxygenation deficit and guided by the FIO_2 required to maintain adequate oxygenation (235,256,257). A PEEP >5 cm H_20 is usually required to avoid lung collapse (261). ARDSnet standard PEEP strategy is shown in Appendix C. The higher PEEP strategy as recommended for ARDS in Recommendation 4 above is shown in Appendix D and comes from the ALVEOLI trial (258)

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 PaO2/FiO2 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 (262). Temporarily raising transpulmonary pressure may facilitate opening atelectatic alveoli to permit gas exchange (261). Such maneuvers, however, could also overdistend aerated lung units leading to ventilator induced lung injury and cause temporary hypotension. The application of transient sustained use of continuous positive airway pressure appears to improve oxygenation in patients initially, but these effects are transient in some studies (263). While selected patients with severe hypoxemia may benefit from recruitment maneuvers in conjunction with higher levels of PEEP, there is little evidence to support their routine use in all ARDS patients.(263). Blood pressure and oxygenation should be monitored and recruitment maneuvers discontinued if deterioration in these variables is observed.

Several small studies and one larger study in patients with hypoxemic respiratory failure or acute lung injury have shown that a majority of patients respond to the prone position with improved oxygenation (264-267) None of the individual trials of prone positioning in patients with ALI/ARDS or hypoxemic respiratory failure demonstrated a mortality benefit (268-271). A recent meta-analysis suggested potential benefits for prone positioning in patients with profound hypoxemia with a PaO2/;FiO2 ratio ≤100 mm HG, but not in those with less severe hypoxemia.(271) 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 positionv(271)
Other methods to treat refractory hypoxemia include the use of High Frequency Oscillatory Ventilation, Airway Pressure Release Ventilation and Extracorporeal Membrane Oxygenation (272). These therapies may be considered as rescue therapies in centers with expertise and experience with their use (262,272-275).Inhaled nitric oxide does not improve mortality in patients with ARDS and should not be routinely used (276)...

7, We recommend 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)..

Rationale. The semi-recumbent position has been demonstrated to decrease the incidence of ventilator-associated pneumonia (VAP)(277). 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-recumbant position (277). However, the bed position was only monitored once a day, and patients who did not achieve the desired bed elevation were not included in the analysis (277). A recent study did not show a difference in incidence of VAP between patients maintained in supine and semirecumbent positions (278). In this study, 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 (278). 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 ALI/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, reduced requirements for sedation. Two RCTs in patients with acute respiratory failure demonstrate improved outcome with the use of NIV in patients when it can be used successfully (279,280). Unfortunately, only a small percentage of patients with sepsis life-threatening hypoxemia can be managed in this way (281,282).

Patients should be considered for NIV in sepsis-induced ALI/ARDS if responsive to relatively low levels of pressure support and PEEP with stable hemodynamics, can be made comfortable, and are easily arousable; who are able to protect the airway and spontaneously clear the airway of secretions; and who

are anticipated to recover rapidly from the precipitating insult (281,282,). 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 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).

Rationale. Spontaneous breathing trial (SBT) options include a low level of pressure support, continuous positive airway pressure (≈5 cm H2O), or a T-piece. Recent studies demonstrate that daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation (283, 284). These spontaneous breathing trials should be conducted in conjunction with a spontaneous awakening trial (SAT) (285). 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 ALI/ARDS (grade 1A).

Rationale. While insertion of a pulmonary artery (PA) catheter may provide useful information on a patient's volume status and cardiac function, potential benefits of such information may be confounded by differences in interpretation of results (286-288), lack of correlation of PA occlusion pressures with clinical response (289), and absence of a proven strategy to use catheter results to improve patient outcomes (174). Two multicenter randomized trials, one in patients with shock or acute lung injury (290) and one in patients with acute lung injury (291), failed to show benefit with the routine use of pulmonary artery catheters in patients with acute lung injury. In addition, other studies in different types of critically ill patients have failed to show definitive benefit with routine use of the PA catheter (292-294). 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 (293,295).

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

Rationale. Mechanisms for the development of pulmonary edema in patients with acute lung injury include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure (296). Small prospective studies in patients with critical illness and acute lung injury have suggested that less weight gain is associated with improved oxygenation (297) and fewer days of mechanical ventilation (298,299). Use of a fluid-conservative strategy directed at minimizing fluid infusion and weight gain in patients with acute lung injury based on either a central venous catheter (central venous pressure <4mm Hg) or a PA catheter (pulmonary artery wedge pressure <8mm Hg) along with clinical variables to guide treatment strategies led to fewer days of mechanical ventilation and reduced length of ICU stay without altering the incidence of renal failure or mortality rates (300). Of note, this strategy was only used in patients with established acute lung injury, some of whom had shock present during the ICU stay and active attempts to reduce fluid volume were conducted only during periods free from shock.

12. In the absence of specific indications such as bronchospasm, we recommend against the use of beta 2-agonists for treatment of ALI/ARDS in patients with sepsis- induced ARDS. (grade 1B)

Rationale. Patients with sepsis –induced acute lung injury often develop increased vascular permeability. Preclincial and early clinical data suggest that beta-adrenergic agonists may speed resorption of alveolar edema(301). Two randomized clinical trials studied the affect of beta-agonists in patients with acute lung injury (302, 303). A randomized controlled trial of aerosolized albuterol versus placebo in 282 patients with acute lung injury was stopped for futility (302). Patients receiving albuterol had higher heart rates on day 2, and a trend toward decreased ventilator –free days (days alive and off the ventilator). The number of patients who died before discharge was (23.0 versus 17.7) in the albuterol versus placebo treated patients. Of note, more than half of the patients enrolled in this trial had pulmonary or nonpulmonary sepsis as the cause of their ALI (302).

The use of intravenous salbutamol was tested in the BALTI-2 trial. 326 Patients with ARDS, 251 of whom had pulmonary or nonpulmonary sepsis as cause, were randomized to get intravenous salbutatmol , 15 µg/kg of ideal body weight or placebo for up to 7 days (303). 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. (303)

Beta-2 agonists have specific indications such as treatment of bronchospasm, auto-PEEP and hyperkalemia. In the absence of these conditions, we recommend against the routine use of beta-

agonists, either in intravenous or aerosolized form, for the treatment of patients with sepsis induced ALI (285).

P. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. We recommend 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 length of stay (304-306). The use of protocols for sedation is one method to limit sedation use and a randomized, controlled clinical trial found that protocol use reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates (306).While these 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 (306). A randomized, controlled clinical trial found that patients treated with intravenous morphine boluses preferentially, with short-term propofol infusions for rescue therapy only, had significantly more days without ventilation, shorter stay in ICU and hospital, than patients who received propofol infusions in addition to bolus morphine (307). However, agitated delirium was more frequent in the intervention group. Several studies have used a specific sedation scale to titrate sedative use (308,309).

Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily sedative interruption, and systematic titration to a predefined end point have been demonstrated to decrease the duration of mechanical ventilation (285,306, 311)). Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because neuromuscular blocking drugs must first be discontinued. 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 (311). Similarly, a prospective, controlled study in 128 mechanically ventilated adults receiving continuous intravenous sedation demonstrated that a daily interruption in the continuous sedative infusion until the patient was awake decreased the duration of mechanical ventilation and ICU length of stay (312)

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 one-year mortality (285). Many patients may tolerate mechanical ventilation without the use of continuous infusion of sedatives (307). Systematic (protocolized) titration to a predefined end point has also been shown to alter outcome (306). 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 (313). Thus, the benefits of daily interruption of sedation appear to outweigh the risks. These benefits includeshorter duration of mechanical ventilation and ICU stay,decreased mortality, better assessment of neurologic function, increased ability to participate in early physical rehabilitation, and reduced costs (285,314).

2. We recommend that NMBAs be avoided if possible in the septic patient *without ALI/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 NMBA of not greater than 48 hours for patients *with* early, severe sepsis-induced ARDS (grade 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 general 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 (315). When appropriately used, NMBAs may improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures (316). Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow (317). 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 (318).

A recent randomized clinical trial of continuous infusions of cisatracurium in patients with early, severe ARDS showed improved adjusted survival rates and more organ failure-free days compared with placebo treated patients (319) without an increased risk in ICU-acquired weakness. Of note, 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 (319,320). It is not known whether another NMBA would have similar effects. While many of the patients enrolled into this trial appear 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 online..

An association between NMBA use and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population (316, 321-323). The mechanisms by which NMBAs produced or contribute to myopathies and neuropathies in critically ill patients are presently unknown. Although no studies exist 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 (316).

Only one prospective RCT has evaluated peripheral nerve stimulation vs standard clinical assessment in ICU patients. Rudis (324) randomized 77 critically ill patients requiring neuromuscular blockade in the ICU 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 (325-326).

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 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. We recommendblood 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. We recommend thatglucose levels obtained with point-of-care testing of capillary blood be interpreted withcaution, as such measurements may not accurately estimate arterial blood or plasma glucose values.

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 80–110 mg/dL (327). (A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU LOS of more than3 days in three medical ICUs and overall mortality was not reduced. [328].

Since these studies (327,328) and the previous Surviving Sepsis Guidelines (7), several RCTs (129, 329-333) and meta-analyses (334,335) of intensive insulin therapy have been performed. The RCTs studied mixed populations of surgical and medical ICU patients (128,329-333). The studies found that intensive insulin therapy did not significantly decrease mortality (129,186,329-331,334) whereas the NICE-SUGAR trial demonstrated an increased mortality (332). All studies reported a much higher incidence of severe hypoglycemia (glucose ≤40mg/dL) (6-29%) with intense insulin therapy. Several meta-analyses confirmed that intense insulin therapy was not associated with a mortality benefit in surgical, medical or mixed ICU patients (335-337). The Griesdale meta-analysis (335) using between trial comparisons driven mainly by the van den Berghe Study (327) found that intense insulin therapy was beneficial in surgical ICU patients [risk ratio 0.63 (0.44-0.91)], whereas the Friedrich meta-analysis (337) 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 intense insulin therapy. Interestingly, the RCTs that noted benefit from intense insulin therapy (129,327-330) compared intensive insulin therapy to high

controls (180-200mg/dL) [odds ratio 0.89 (0.73-1.09)], whereas those that did not demonstrate benefit (331,333,334) compared intensive therapy to moderate control (108-180 mg/dL) [odds ratio 1.14 (1.02-1.26) Online Appendix H.

The trigger to start an insulin protocol for blood glucose levels >180 mg/dL with an upper target blood glucose < 180 mg/dL derive from the NICE-SUGAR study (332) which used these values for commencing 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, the American Diabetes Association, the American Heart Association, the American College of Physicians,,and the Society of Critical Care Medicine have recently published consensus statements for glycemic control of hospitalized patients (338-342). These statements usually targeted glucose levels between 140 and 180 mg/dL. As there is no evidence that targets of 140-180 mg/d are different from targets of 110 to140 mg/dl, the present recommendations use an upper target blood glucose <180 mg/dL without a lower target other than hypoglycemia. Treatment should be aimed to 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 (333). Balanced nutrition may be associated with a reduced risk of hypoglycemia (343). Recent studies have suggested that the importance of variability in glucose levels over time is an important determinant of mortality (344-346). Hyperglycemia and glucose variability seem to be unassociated with increased mortality in diabetic patients as compared to non-diabetic patients (347, 348).

Several factors may affect the accuracy and reproducibility of point-of-care testing of blood capillary blood glucose, including the type and model of the device used, user expertise, and patient factors, including hematocrit (false elevation with anemia), PaO_2, and drugs (349). Plasma glucose values by capillary point of care testing have been found to be inaccurate with frequent false elevations (350,351) over the range of glucose levels (351) but especially in the hypoglycemic (350, 352) and hyperglycemic glucose ranges (352) and in hypotensive patients (353) or patients receiving catecholamines (354). A

review of 12 published insulin infusion protocols for critically ill patients showed wide variability in insulin dose recommendations and variable glucose control (355). 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. This conclusion is supported by the wide variability in hypoglycemia rates reported with protocols (129,327-334). 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 these trials before the efficacy signal, if any, can be determined. Recently, several studies have suggested that computer-based algorithms result in tighter glycemic control with a reduced risk of hypoglycemia (356,357). Further study of protocols that have been validated to be safe and effective for controlling blood glucose concentrations and blood glucose 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 (358-364), 2 meta-analyses (366,367) reported the absence of significant difference in hospital mortality between patients who receive continuous and intermittent renal replacement therapies. This absence of apparent benefit of one modality over the other persists even when the analysis is restricted to only RCT studies (367). To date, 5 prospective RCTs have been published (368-372). Four of them found no significant difference in mortality (369-372). One study found significantly higher mortality in the continuous treatment group (368), 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 (368). Most studies

comparing modes of renal replacement in the critically ill have included a small number of patients and some major weaknesses (randomization failure, modifications of therapeutic protocol during the study period, combination of different types of continuous renal replacement therapies, small number of heterogeneous groups of patients enrolled). The most recent and largest RCT (372) enrolled 360 patients and found no significant difference in survival between the 2 groups. Moreover, there is no current evidence to support the use of continuous therapies in sepsis independent of renal replacement needs. Concerning the hemodynamic tolerance of each method, no current evidence exists to support a better tolerance with continuous treatments. Only 3 prospective studies (370,373) have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion (373) and no survival benefit (370). Four other prospective studies did not find any significant difference in mean arterial pressure or drop in systolic pressure between the two methods (369,371,372,374). Concerning fluid balance management, 2 studies reported a significant improvement in goal achievement with continuous methods (368,370). In summary, current evidence is insufficient to draw strong conclusions regarding the mode of replacement therapy for acute renal failure in septic patients.

Four RCTs have addressed whether the dose of continuous renal replacement affects outcomes in patients with acute renal failure (375-378). Three found improved mortality in patients receiving higher doses of renal replacement (375,377,378), while one (376) did not. None of these trials was conducted specifically in patients with sepsis. Although the weight of current evidence suggests that higher doses of renal replacement may be associated with improved outcomes, these results may not be easily generalizable. Two large multicenter randomized trials comparing the dose of renal replacement (ATN in the United States and RENAL in Australia and New Zealand) failed to show benefit of more aggressive renal replacement dosing. A typical dose for CRRT, would be 20-25 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 of utility in some situations during utilization of permissive hypercapnia in limiting tidal volume in ARDS (see Mechanical Ventilation of ARDS section), no evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic academia 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 (379,380). The number of patients with pH <7.15 in these studies was small. Bicarbonate administration has been associated with sodium and fluid overload, an increase in lactate and PCO_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 twice daily UFH and versus three times daily UFH (grade 2C) .

. If creatinine clearance is <30 ml/min and LMWH is used, we recommend use of dalteparin (grade 1A) or another form ofof LMWH that has a low degree ofof 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 for heparin use (eg,, thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) not

receive pharmacoprophylaxis (grade 1B), but 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 DVT (381). It is logical that patients with severe sepsis would be similar to or at higher risk than the general ICU population. The consequences of VTE in the setting of sepsis(increased risk of potentially fatal PEs in an already hemodynamically compromised patient) are dire. Therefore, prevention of VTE is highly desirable, especially if it can be done safely and effectively. VTE prophylaxis is generally effective. In particular, nine placebo-controlled RCTs ofVTE prophylaxis in general populations of acutely ill patients exist (382-390). All 9 trials showed reduction in DVT or pulmonary embolism, a benefit that is also supported by meta-analyses (391, 392).Thus, the evidence strongly supports the value of VTE prophylazxis (grade 1A). The prevalence of infection/sepsis was 17% in those studies in which this could be ascertained. One study investigated ICU patients only, In that trial, 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 of B. Because the risk of administration to the patient is small, the gravity of not administeringmay be great, and the cost is low, the strength of the recommendation is strong (1).

Deciding how to provide prophylaxis is decidedly more difficult. A recently published RCT by the Canadian Critical Care Trials Group compared UFH (5000U twice daily) to LMWH (dalteparin, 5000U once per day and a second placebo injection to ensure parallel-group equivalence) (393).There was not a statistically significant difference in asymptomatic DVTs between the 2 groups (hazard ratio: 0.92, 95% CI: 0.68-1.23. P = 0.57). However, the proportion of patients with pulmonary embolism diagnosed when patients had CT scans showing filling defects, high-probability VQ scans, or on 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

in critically ill patients when compared to UFH administered twice daily. The study included septic patients. Therefore, the evidence supporting the use of dalteparin over twice daily UFH in critically ill, and perhaps septic, patiens is strong (A). Similarly, a meta-analysis of acutely ill, general medical patients comparing UFH 2 times daily and 3 times daily demonstrated that UFH administered three times daily more effectively prevented VTE but twice daily dosing produced less bleeding(394). There are critically ill and, indeed, septic patients included in these analyses but the numbers are unclear. Nonetheless, the evidence supporting the use of three times daily, as opposed to twice daily, UFH dosing in preventing VTE in acutely ill medical patients is strong (A). However, comparing LMWH to twice daily UFH or twice daily UFH to three times daily UFH in sepsis requires extrapolation, downgrading the data (B). There are no data directly comparing LMWH to UFH administered 3 times a day nor are there studies directly comparing twice daily and three times 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 conducted a study of 120 critically ill patients with acute kidney injury (creatinine clearance < 30 ml/min) who received VTE prophylaxis with dalteparin 5000IU 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 (395). 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 clear and is safe (grade 1A)..

Mechanical methods (intermittent compression devices and graduated compression stockings) are recommended when anticoagulation is contraindicated (396-398). A meta-analysis of 11 studies, including 6 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 (399). The included studies were underpowered to

determine if combined therapy were superior to pharmacologic therapy alone. This analysis did not focus on sepsis or critically ill patients but included studies of prophylaxis for patients 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 (393,400-402). 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 (403)..

U. Stress Ulcer Prophylaxis

1. We recommend that 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, we suggest the use of proton pump inhibitors rather than histamine 2 receptor antagonists (H2RA) (grade 2C)

3. We suggest that patients without risk factors do 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 GI bleeds in general ICU populations enrolled 20- 25% of patients with sepsis (404-407). This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the risk factors for gastrointestinal bleeding (coagulopathy, mechanical ventilation for at least 48 hours, possibly hypotension) are frequently present in patients with severe sepsis and septic shock (408,409). Patients without these risk factors are unlikely (0.2%, 95% CI 0.02-0.5%) to have clinically important bleeding (408).

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 (410-412). The benefit of prevention of upper GI bleed must be weighed against the potential (not proven) effect of increased stomach pH on greater incidence of ventilator-associated pneumonia and *Clostridium difficile* infection (410,413,414) (See online Summary of Evidence Tablesfor effects of treatments on specific outcomes). We considered the possibility of less benefit and more harm of prophylaxis among patients

receiving enteral nutrition as an exploratory hypothesis (as did the authors of the meta-analysis suggesting such a possibility) (412) but decided to provide one recommendation while lowering quality of evidence (412). The balance of benefits and risks may thus depend on the individual patient's characteristics as well as on local epidemiology of VAP and *C. difficile* infections. The rationale for considering only suppression of acid production (and not sulcrafate) is based on the study of 1,200 patients by Cook comparing H2 blockers and sulcrafate (415). Recent meta-analyses provide low quality evidence suggesting more effective GI bleeding protection with the use of proton pump inhibitors (PPI) in comparison to H2RA (416-418). Patients should be periodically evaluated for continued need for prophylaxis.

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HV. 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 hours 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 kilocalories 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 sepis/septic shock (grade 2B).

4. We suggest using nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

*Rationale.*There are theoretical advantages to early enteral nutrition regarding integrity of gut mucosa and prevention of bacterial translocation and organ dysfunction. However, there is also some concern about the risk of ischemia with early feeding, mainly in hemodynamically unstable patients.

Unfortunately, no clinical trial 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 intervention and control groups, all with low methodological quality (419-428). None of those trials was individually powered for mortality, with very low mortality rates (419-421,424,427). 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 (419-431).. Of note, although there was no consistent effect on mortality, there was some evidence of benefit from some early enteral feeding on secondary outcomes, such as reduced incidence of infectious complications (419,423,427,429-431), reduced length of mechanical ventilation (422,428) and reduced ICU (422, 428) and hospital stay (429). 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 some 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, there was no effect on mortality (432-435, one reported fewer infectious complications (432) and others reported increased diarrhea and gastric residuals (434-435) and increased incidence of infectious complications with full caloric feeding (433. In one study, mortality was higher with higher feeding, but differences in feeding strategies were modest and sample size was small (436). Therefore, there is insufficient evidence to support an early target of full caloric intake and, indeed, some possibility of harm. Underfeeding (60-70% of target) or trophic feeding (upper limit of 500 kcal) are probably better nutritional strategies 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 2 recent studies

used a range of 240-480 (434,435). Of note, 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) (437), and there are currently 8 meta-analyses (430,438-444) . Two of the meta-analyses summarize parenteral nutrition vs fasting or intravenous glucose (438,439) and 6 summarize parenteral versus enteral nutrition (430,440,441,444), 2 of which attempt to explore the effect of early enteral nutrition (442,443). Recently, a study much larger than most prior nutrition trials compared ICU patients randomized to early use of parenteral nutrition to augment enteral feeding versus enteral feeding with only late initiation of parenteral nutrition if necessary (445).

There is no direct evidence regarding the benefits or harm of parenteral nutrition in the first 48 hours in sepsis. Rather, the evidence is generated predominantly from surgical, burns, 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 (443). Several suggested parenteral nutrition had higher infectious complications compared both to fasting or intravenous glucose and to enteral nutrition (430,439,440,432,443). Enteral feeding was associated with a higher rate of enteral complications (eg, diarrhea) than parenteral nutrition (439). Of note, the use of parenteral nutrition to supplement enteral feeding was also summarized by Dhaliwal et al, who also reported no benefit (441). The Casaer et al trial reported that early initiation of parenteral nutrition led to longer hospital and ICU length of stay, 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 sepsis (445).

Therefore, there are no studies suggesting any superiority of TPN over enteral alone in the first 24 hours. In fact, there is a suggestion that enteral nutrition (EN) may in fact be superior to TPN regarding 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. However, few specifically addressed the early use of such supplements in sepsis.

Four meta-analyses evaluated immune-enhancing nutrition and found no difference in mortality, neither in surgical nor medical patients (446-449). However, they analyzed all studies together, regardless of the immunocomponent used, which could have compromised their conclusions. There are also other individual studies analyzing diets with a mix of arginine, glutamine, antioxidants and/or omega-3 with negative results (450,459) including a small study in septic patients showing a non-significant increase in ICU mortality (453).

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 (453,454). To date, human trials of L-arginine supplementation have generally been small and reported variable effects on mortality (455-459). The only study in septic patients showed improved survival, but there are limitations in study design (456). Other studies suggested no benefit (457-459) 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 (455,456) and length of stay (455). However, the relevance of these findings in the face of potential harm is unclear.

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 (454,454). However, the clinical significance of these findings is not clearly established.

Although a previous meta-analysis showed mortality reduction (430), 4 other meta-analyses did not (460-463). Previous small studies not included in those meta-analyses have similar results (464,465). Three

recent well-designed studies also failed to show a mortality benefit in the primary analyses (228,466,467). Again, however, none focused specifically on septic patients. Two small studies on septic patients showed no benefit in mortality, (468,469) with significant reduction in infectious complications (468) and a faster recovery of organ dysfunction (469). Some previous individual studies and meta-analyses showed positive secondary outcomes, such as reduction in infectious morbidity (462,463,466) and organ dysfunction (463). 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 (228) or organ dysfunction (466,467), even with parenteral glutamine. An ongoing trial (REDOXS, www.clinicaltrials.gov/ NCT00133978) of 1200 patients will test both enteral and parenteral glutamine and antioxidant supplementation in critically ill mechanically ventilated patients (470). 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 linolenic acid (GLA) are eicosanoid precursors. The prostaglandins, leukotrienes, and thrombaxanes produced from EPA/GLA are less potent than their arachidonic acid-derived equivalents, reducing the pro-inflammatory impact on the immune response (453,454). 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 (471). However, only one study was in septic patients (472), none was individually powered for mortality (473,474), and all 3 used a diet with high omega-6 lipid content in the control group, which is not usual standard of care in the critically ill. Recently, the authors who first reported reduced mortality in sepsis (472) reported a follow-up multicenter study again finding improvement in non-mortality outcomes, though notably with no demonstrable effect on mortality (475). Other studies using enteral (476-478) or parenteral (479-481) fish oil failed to confirm these findings in general critical illness or acute lung injury.

Thus, at this point, there are no large, reproducible findings suggesting a clear benefit to the use of immunomodulating nutritional supplements in sepsis, though larger trials are on-going.

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 hours 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 family's desire (482). Physicians have different end-of-life practices based on their region of practice, culture, and religion (483). 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 (484). Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care along with prognosis into treatment plans (485). Additionally, discussing 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 (486,487). 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 quality of care (488,489). The use of proactive family care conferences to identify advanced directives and treatment goals within 72 hours of ICU admission has been demonstrated to promote communication and understanding between the patient's family and the treating team; improve family satisfaction; decrease stress, anxiety, and depression in surviving relatives; facilitate end-of-life decision making; and shorten length of stay in the ICU for patients who die in the ICU (490-495). 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 (496). Additionally, the integration of advanced care planning and palliative care in the ICU focused on pain management, symptom control, and family support has been shown to improve symptom management and patient comfort, and improve family communication (485,491,497).

PEDIATRIC CONSIDERATIONS IN SEVERE SEPSIS

While sepsis in children is a major cause of mortality in industrialized countries with state of the art intensive care units, the overall mortality from severe sepsis is much lower than that in adults, estimated at about 2-10% (498-500). Severe sepsis hospital mortality is 2% in previously healthy children and 8% in chronically ill children in the US (498). 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 cut-offs (501,502). This SSC document provides recommendations only for term newborns and children in the industrialized resource-rich setting with full access to mechanical ventilation and intensive care units. .

A. Initial Resuscitation

1. We suggest starting with face mask oxygen, or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP) for respiratory distress and hypoxemia. 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 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, increased intrathoracic pressure can reduce venous return and lead to worsening shock if a patient is not volume loaded. In

patients who desaturate despite face mask oxygen, high flow nasal cannula oxygen or NP CPAP can be used to increase functional residual capacity and reduce work of breathing allowing for establishment of intravenous or intra-osseous access for fluid resuscitation and peripheral inotrope delivery (503, 504). 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 (505,506). Because attainment of central access is more difficult in children than adults, reliance on peripheral or intra-osseus access can be substituted until and unless central access is available.

2. We suggest that the initial therapeutic end points of resuscitation of septic shock be capillary refill of $\leq$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 (CI) between 3.3 and 6.0 $L/min/m^2$ should be targeted thereafter (grade 2C).
Rationale. Adult guidelines recommend lactate clearance as well, but children commonly have normal lactate levels with septic shock. Regarding the many modalities used to measure $SCVO_2$ and CI, the specific use of one over the other is left to the practitoner's discretion (507-513).
3. We recommend following ACCM-PALS guidelines for the management of septic shock (grade 1C).
Rationale. The ACCM-PALS guidelines are summarized in Figure 2. (511-513)
4. We recommend evaluating for and reversing pneumothorax, pericardial tamponade, intra-abdominal hypertension, or endocrine emergencies in patients with refractory shock (grade 1C).
Rationale. Intra-abdominal hypertension is diagnosed by a bladder pressure >12 mm Hg (514). Peritoneal paracentesis should be considered when the bladder pressure is >15 mmHg and surgical decompression is warranted if the intra-abdominal pressure is > 0 mm Hg (515-516). Endocrine emergencies include hypoadrenalism and hypothyroidism.

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 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).

Rationale. Vascular access and blood drawing is more difficult in newborns and children. Antimicrobials can be given intra-muscularly or orally (if tolerated) when access is not attainable until intravenous line access is available (517-520).

2. We suggest clindamycin and anti-toxin therapies for toxic shock syndromes with refractory hypotension (grade 2D).

Rationale. Children are more prone to toxic shock than adults because of 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 is unclear but it may be considered in refractory toxic shock syndrome (521-528).

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

Rationale. Debridement and source control is paramount in severe sepsis and septic shock. Among others necrotizing pneumonia, necrotizing fasciitis, gangrenous myonecrosis, empyema, and abcesses can all require debridement or drainage. Perforated viscus requires repair and peritoneal wash out. Delay in use of appropriate antibiotic, inadequate source control, and removal of infected devices are associated with increased mortality in a synergistic manner (529-539).

4. *Clostridium 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 perfomed, enteral treatment should be considered until clinical improvement is ascertained (540-542).

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 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 hepatomegly 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).

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 (543-545). In the industrialized world, 2 before-and-after studies observed 10-fold reductions in mortality when children with purpura / meningococcal septic shock were treated in the community emergency department with fluid boluses, inotropes, and mechanical ventilation (546,547). One randomized trial showed a reduction in septic shock mortality from 40% to 12 % when increased fluid boluses, blood, and inotropes were given to attain a $SCVO_2$ monitor goal > 70% (512). A before-and-after quality improvement study showed reduction in severe sepsis mortality from 4.0% to 2.4% with earlier delivery of fluid boluses and antibiotics in the first hour in a pediatric emergencv department directed to reversing clinical signs of shock noted above (548). By contrast, in a randomized controlled trial of children with severe infection in the sub-Saharan severe malarial anemia belt where there was no accces to inotropes, mechanical ventilation, or intensive care, there was an increased mortality when fluid boluses were given (without regard to the presence of hepatomegaly or rales, or clinical goals) compared to provision of intravenous fluid at maintenance rate and 20 mL/kg blood transfusion over 2 hours for children with a Hgb < 5 g/dL (549).

Children normally have a lower blood pressure than adults, and fall in blood pressure can be prevented by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Thus fluid resuscitation is recommended even for both normotensive and hypotensive children in hypovolemic shock (543-556). 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 40–60 mL/kg or more; however, if these signs are present, then fluid administration should be ceased and diuretics should be given. Inotrope infusions and mechnical 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 (555, 556). 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 (557). A child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the hemodynamic state (557). Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion. In the case of extremely low systemic vascular resistance despite the use of norepinephrine, vasopressin and terlipressin have been described in a number of case reports. Yet evidence for the use of vasopressin or terlipressin in pediatric sepsis, as well as safety data, are still lacking. Indeed, 2 RCTs showed no benefit in outcome with use of vasopressin or terlipressin in children (558-561). Interestingly, while vasopressin levels are reduced in adults with septic shock, such levels seem to vary quite extensively in children. When vasopressors are used for refractory hypotension, the addition of inotropes is commonly needed to maintain adequate cardiac output (511, 512, 557).

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. The use of 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 2 RCTs, pentoxyfilline reduced mortality from severe sepsis in newborns (511, 562-571).

E. Extracorporeal Membrane Oxygenation (ECMO) and Inhaled Nitric Oxide

1. We suggest consideration of ECMO for pediatric septic shock in the presence of refractory respiratory failure (grade 2C).

Rationale. Survival from refractory shock or respiratory failure with sepsis and use of ECMO is 80% in neonates and 50% in children. Best outcomes of 78% survival have been reported in children with septic shock who underwent open chest cannulation rather than peripheral cannulation (similar to outcomes in neonates with neck cannulation). Use of venovenous ECMO as part of the strategy for H1N1 mediated ARDS in older children resulted in an 80% survival (511,572-578).

F. Corticosteroids

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

Rationale. Approximately 25% of children with septic shock have absolute adrenal insufficiency defined by a peak cortisol <18 µg/dL after the corticotropin stimulation test, or a basal cortisol level <4 µg/dL. Patients at risk for absolute adrenal insufficiency include children with severe septic shock and purpura, children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. Initial treatment is hydrocortisone infusion at stress-dose (50 mg/m^2/24 hrs); 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 hours of presentation, Obtaining a serum cortisol level at the time of empiric hydrocortisone may be helpful. (579-584).

G. Protein C and Activated Protein Concentrate

See section in Adjuvant Therapy related to the history of rhAPC.

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 lack of clear evidence of equivalence in outcomes with the restrictive strategy (585, 586). Blood transfusion is recommended by the World Health Organization (WHO) for severe anemia, Hgb <5 g/dL, and acidosis. A RCT of early goal-directed therapy for pediatric septic shock using the threshold hemoglobin of 10 g/dL Hgb for patients with a $SVCO_2$ saturation <70% in the first 72 hours of pediatric intensive care unit (PICU) admission showed improved survival in the multimodal intervention arm (512).

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 FFP contains protein C, anti-thrombin III, and other anticoagulant proteins. Rapid resuscitation of shock reverses most disseminated intravascular coagulation; however, in some children purpura progresses in part due to critical consumption of anti-thrombotic proteins (eg, protein C, antithrombin III, ADAMTS 13). Plasma is infused with the goal of correcting prolonged PT/PTT times and halting purpura. Large volumes of plasma require concomitant use of diuretics, CRRT, or plasma exchange to prevent >10% fluid overload (587-612).

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 FRC and maintain oxygenation, and peak pressures >30-35cm H_2O to attain effective tidal volumes of 6-8 mL/kg with adequate CO_2 removal. In these patients, physicians generally transition from conventional pressure control ventilation to pressure release ventilation (APRV) or to high frequency oscillatory ventilation

(HFOV). 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 5cm H_2O higher than that used with conventional ventilation. This can reduce venous return leading to greater need for fluid resuscitation and vasopressor requirements (613-617)

J. Sedation/Analgesia/DrugToxicities

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, it should be noted that propofol should not be used for long-term sedation in children <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 (618-621).

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 (622).

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 because some hyperglycemic children make no insulin whereas others are insulin resistant (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 4–6 $mg \cdot kg^{-1} \cdot min^{-1}$ 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. A recent RCT of strict glycemic control compared to moderate control using insulin in a PICU population found a reduction in mortality with an increase in hypoglycemia. The authors plan to report neurologic outcomes in a 1-year follow-up cohort. 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 1) relative lack of glycogen stores and muscle mass for gluconeogenesis, and 2) the heterogeneity of the population with some excreting no endogenous insulin and others demonstrating high insulin levels and insulin resistance (623-629).

L.. Diuretics and Renal Replacement Therapy

1. We suggest use of diuretics to reverse fluid overload, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 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 (550,554) A retrospective study of 113 critically ill children with MODS reported that patients with less fluid overload before CVVH had better survival (630-632),

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 on the efficacy of Ultra Fractionated Heparin or Low Molecular Weight Heparin prophylaxis to prevent catheter-related DVT in children in the ICU exist (633,634).

N. Stress Ulcer Prophylaxis

We make no graded recommendations on stress ulcer prophylaxis.

Rationale. Studies have shown that clinically important gastrointestinal bleeding in children occurs at rates similar to adults. Stress ulcer prophylaxis strategy is commonly used in mechanically ventilated children, usually with H_2 blockers or proton pump inhibitors. Its effect is not known (635,636.)

O. Nutrition

1. Enteral nutrition should be given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

Rationale. D10% (always with Na containing solution in children) at maintenance rate provides the glucose delivery requirements for newborns and children (637). 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. Since publication of the 2008 guidelines, there has been some additional evidence that allows more certainty with which we make severe sepsis recommendations; however, more programmatic clinical research in sepsis is essential to optimize these evidence-based medicine recommendations.

New interventions will be proven and, as stated in the current recommendations, established interventions may need modification. This publication represents an ongoing process. The Surviving Sepsis Campaign and the consensus committee members are committed to updating the guidelines regularly as new interventions are tested and published.

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OTHER ACKNOWLEDGMENTS

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310

2. Dellinger RP: Cardiovascular management of septic shock. *Crit Care Med* 2003; 31: 946–955

3. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554

4. Linde-Zwirble WT, Angus DC: Severe sepsis epidemiology: Sampling, selection, and society. *Crit Care* 2004; 8:222–226

5. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007; 35:1414–1415

6. 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

7. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008; 36:296–327. Erratum in: *Crit Care Med* 2008; 36:1394–1396 and *Intensive Care Med* 2008; 34:17–60

8. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873 and *Intensive Care Med* 2004; 30:536–555

9. Guyatt GH, Oxman AD, Vist GE, et al: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926

10. Guyatt GH, Oxman AD, Kunz R, et al: What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; 336:995–998

11. Guyatt GH, Oxman AD, Kunz R, et al: Going from evidence to recommendations. *BMJ* 2008; 336:1049–1051

12. Brożek J, Oxman AD, Schünemann HJ: GRADEpro (Computer Program) Version 3.2 for Windows. Available at http://www.cc-ims.net/revman/gradepro, 2012.

13. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377

14. Early Goal-Directed Therapy Collaborative Group of Zhejiang Province: The effect of early goal-directed therapy on treatment of critical patients with severe sepsis/septic shock: A multi-center, prospective, randomized, controlled study [in Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2010; 6:331–334

15. Levy MM, Dellinger RP, Townsend SR, et al; Surviving Sepsis Campaign: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; 38:367–374

16. Bendjelid K, Romand JA: Fluid responsiveness in mechanically ventilated patients: A review of indices used in intensive care. *Intensive Care Med* 2003; 29:352–360

17. Malbrain ML, Deeren D, De Potter TJ: Intraabdominal hypertension in the critically ill: It is time to pay attention. *Curr Opin Crit Care* 2005; 11:156–171

18. Varpula M, Tallgren M, Saukkonen K, et al: Hemodynamic variables related to outcome in septic shock. *Intensive Care Med* 2005; 31:1066–1071

19. Kortgen A, Niederprum P, Bauer M: Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Crit Care Med* 2006; 34:943–949

20. Sebat F, Johnson D, Musthafa AA, et al: A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. *Chest* 2005; 127:1729–1743

21. Shapiro NI, Howell MD, Talmor D, et al: Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 2006; 34:1025–1032

22. Micek SST, Roubinian N, Heuring T, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34:2707–2713

23. Nguyen HB, Corbett SW, Steele R, et al: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007; 35:1105–1112

24. Shorr AF, Micek ST, Jackson WL Jr, et al: Economic implications of an evidence-based sepsis protocol: Can we improve outcomes and lower costs? *Crit Care Med* 2007; 35:1257–1262

25. Reinhart K, Kuhn HJ, Hartog C, et al: Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med* 2004; 30: 1572–1578

26. Trzeciak S, Dellinger RP, Abate N, et al: Translating research to clinical practice: A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 2006; 129: 225–232

27. Magder S: Central venous pressure: A useful but not so simple measurement. *Crit Care Med* 2006; 34:2224–2227

28. Bendjelid K: Right arterial pressure: Determinant or result of change in venous return? *Chest* 2005; 128:3639–3640

29. Vincent JL, Weil MH: Fluid challenge revisited. *Crit Care Med* 2006; 34:1333–1337

30. Trzeciak S, Dellinger RP, Parrillo JE, et al: Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 2007; 49:88–98

31. De Backer D, Creteur J, Dubois MJ, et al: The effects of dobutamine on microcirculatory alternations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–408

32 Buwalda M, Ince C: Opening the microcirculation: Can vasodilators be useful in sepsis? *Intensive Care Med* 2002; 28:1208–1217

33. Boldt J: Clinical review: Hemodynamic monitoring in the intensive care unit. *Crit Care* 2002; 6:52–59

34. Pinsky MR, Payen D: Functional hemodynamic monitoring. *Crit Care* 2005; 9:566–572

35. Jones AE, Shapiro NI, Trzeciak S, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. *JAMA* 2010; 303:739–746

36. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE Study Group: Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:752–761

37. Cinel I, Dellinger RP: Current treatment of severe sepsis. *Curr Infect Dis Rep* 2006; 8:358–365

38. Moore LJ, Jones SL, Kreiner LA, et al: Validation of a screening tool for the early identification of sepsis. *J Trauma* 2009; 66:1539–1546; discussion 1546–1547

39. Subbe CP, Kruger M, Rutherford P, Gemmel L: Validation of a modified early warning score in medical admissions. *Quart J Med* 2001; 94:521–526

40. Evaluation for Severe Sepsis Screening Tool, Institute for Healthcare Improvement (IHI). http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis/Tools/EvaluationforSevereSepsisScreeningTool.htm

41. Evaluation for severe sepsis screening tool. http://www.survivingsepsis.org/files/Tools/evaluationforseveresepsisscreeningtool.pdf

42. Rivers EP, Ahrens T: Improving outcomes for severe sepsis and septic shock: Tools for early identification of at-risk patients and treatment protocol implementation. *Crit Care Clin* 2008; 23:S1–S47

43. Gao F, Melody T, Daniels DF, et al: The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: A prospective observational study. *Crit Care* 2005; 9:R764–R770

44. Schorr C: Performance improvement in the management of sepsis. *Crit Care Clin* 2009; 25:857–867

45. Girardis M, Rinaldi L, Donno L, et al; Sopravvivere alla Sepsi Group of the Modena-University Hospital: Effects on management and outcome of severe sepsis and septic shock patients admitted to the intensive care unit after implementation of a sepsis program: A pilot study. *Crit Care* 2009; 13:R143

46. Pestaña D, Espinosa E, Sangüesa-Molina JR, et al; REASEP Sepsis Study Group: Compliance with a sepsis bundle and its effect on intensive care unit mortality in surgical septic shock patients. *J Trauma* 2010; 69:1282–1287

47. Berenholtz SM, Pronovost PJ, Ngo K, et al; Core Sepsis Measurement Team: Developing quality measures for sepsis care in the ICU. *Jt Comm J Qual Patient Safety* 2007; 33:559–568

48. Black MD, Schorr C, Levy MM: Knowledge translation and the multifaceted intervention in the intensive care unit. *Crit Care Med* 2012; 40:1324–1328

49. Suarez A, Ferrer R, Artigas A, et al; Edusepsis Study Group: Cost-effectiveness of the Surviving Sepsis Campaign protocol for severe sepsis: A prospective nationwide study in Spain. *Intensive Care Med* 2011; 37:444–452

50. Levy MM, Pronovost PJ, Dellinger RP, et al: Sepsis change bundles: Converting guidelines into meaningful change in behavior and clinical outcome. *Crit Care Med* 2004; 32(Suppl):S595–S597

51. Weinstein MP, Reller LP, Murphy JR, et al: The clinical significance of positive blood cultures: A comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. *Rev Infect Dis* 1983; 5:35–53

52. Blot F, Schmidt E, Nitenberg G, et al: Earlier positivity of central venous versus peripheral blood cultures is highly predictive of catheter-related sepsis. *J Clin Microbiol* 1998; 36:105–109

53. Mermel LA, Maki DG: Detection of bacteremia in adults: Consequences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270–272

54. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388–416

55. Muscedere J, Dodek P, Keenan S, et al: Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Diagnosis and treatment. *J Crit Care* 2008; 23:138–147

56. Giamarellos-Bourboulis EJ, Giannopoulou P, Grecka P, et al: Should procalcitonin be introduced in the diagnostic criteria for the systemic inflammatory response syndrome and sepsis? *J Crit Care* 2004; 19:152–157

57. Uzzan B, Cohen R, Nicolas P, et al: Procalcitonin as a diagnostic test for sepsis in critically ill adults after surgery or trauma: A systematic review and meta-analysis. *Crit Care Med* 2006; 34:1996–2003

58. Tang BM, Eslick GD, Craig JC, et al: Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: Systematic review and meta-analysis. *Lancet Infect Dis* 2007; 7: 210–217

59. Tenover FC: Rapid detection and identification of bacterial pathogens using novel molecular technologies: Infection control and beyond. *Clin Infect Dis* 2007; 44:418–423

60. Klouche M, Schroder U. Rapid methods for diagnosis of bloodstream infections. *Clin Chem Lab Med* 2008; 46:888–908

61. Tissari P, Zumla A, Tarkka E, et al: Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: An observational study. *Lancet* 2010 Jan 16; 375:224–230

62. Alam FF, Mustafa AS, Khan ZU: Comparative evaluation of (1, 3)-beta-D-glucan, mannan and anti-mannan antibodies, and Candida species-specific snPCR in patients with candidemia. *BMC Infect Dis* 2007; 7:103

63. Oliveri S, Trovato L, Betta P, et al: Experience with the Platelia Candida ELISA for the diagnosis of invasive candidosis in neonatal patients. *Clin Microbiol Infect* 2008; 14:391–393

64. Sendid B, Poirot JL, Tabouret M, et al: Combined detection of mannanaemia and antimannan antibodies as a strategy for the diagnosis of systemic infection caused by pathogenic Candida species. *J Med Microbiol* 2002; 51:433–442

65. Sendid B, Jouault T, Coudriau R, et al: Increased sensitivity of mannanemia detection tests by joint detection of alpha- and beta-linked oligomannosides during experimental and human systemic candidiasis. *J Clin Microbiol* 2004; 42:164–171

66. Sendid B, Dotan N, Nseir S, et al: Antibodies against glucan, chitin, and Saccharomyces cerevisiae mannan as new biomarkers of Candida albicans infection that complement tests based on C albicans mannan. *Clin Vaccine Immunol* 2008; 15:1868–1877

67. Yera H, Sendid B, Francois N, et al: Contribution of serological tests and blood culture to the early diagnosis of systemic candidiasis. *Eur J Clin Microbiol Infect Dis* 2001; 20:864–870

68. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596

69. Morrell M, Fraser VJ, Kollef MH: Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005; 49:3640–3645

70. Ferrer R, Artigas A, Suarez D, et al, for the Edusepsis Study Group: Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009; 180:861–866

71. Barie PS, Hydo LJ, Shou J, et al: Influence of antibiotic therapy on mortality of critical illness caused or complicated by infection. *Surg Infect* 2005; 6:41–54

72. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, et al: Impact of the surviving sepsis protocols on hospital length of stay and mortality in septic shock patients: Results of a three-year follow-up quasi-experimental study. *Crit Care Med* 2010; 38:1036–1043

73. Puskarich MA, Trzeciak S, Shapiro MI, et al: Association between timing of antibiotic administration and mortality from septic shock inpatients treated with a quantitative resuscitation protocol. *Crit Care Med* 2011; 39:2066–2071

74. El Solh AA, Akinnusi ME, Alsawalha LN, et al: Outcome of septic shock in older adults after implementation of the sepsis "Bundle." *J Am Geriat Soc* 2008; 56:272–278

75. Gurnani PK, Patel GP, Crank CW, et al: Impact of the implementation of a sepsis protocol for the management of fluid-refractory septic shock: A single-center, before-and-after study. *Clin Therap* 2010; 32:1285–1293

76. Nguyen HB, Corbett SW, Steele R, et al: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007; 35:1105–1112

77. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics* 2011; 127: e1585–e1592

78. Barochia AV, Cui X, Vitberg D, et al: Bundled care for septic shock: An analysis of clinical trials. *Crit Care Med* 2010; 38:668–678

79. Pappas PG, Kauffman CA, Andes D, et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:503–535

80. Leibovici L, Shraga I, Drucker M, et al: The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; 244:379–386

81. Ibrahim EH, Sherman G, Ward S, et al: The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118:146–155

82. Ali MZ, Goetz MB: A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; 24:796–809

83. Amsden GW, Ballow CH, Bertino JS: Pharmacokinetics and pharmacodynamics of anti-infective agents. *In:* Principles and Practice of Infectious Diseases. 7th ed. Mandell GL, Bennett JE, Dolin R (Eds). Philadelphia, Churchill Livingstone, 2010, pp 297–307

84. Heyland D K, Reynolds S, Jiang X, et al: Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation. *Crit Care Med* 2011; 39:1792–1799

85. Jensen JU, Hein L, Lundgren B, et al: Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial. *Crit Care Med* 2011; 39:2048–2058.

86. Brunkhorst FM, Oppert M, Marx G, et al: Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis. *JAMA* 2012; 307:2390–2399

87. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only of death: A meta-analytic/meta-regression study. *Crit Care Med* 2010; 38:1651–1664

88. Kumar A, Zarychanski R, Light B, et al: Early combination antibiotic therapy yields improved survival compared with monotherapy: A propensity-matched analysis. *Crit Care Med* 2010; 38:1773–1785

89. Micek ST, Welch EC, Khan J, et al: Empiric combination antimicrobial therapy is associated with improved outcome against sepsis due to gram-negative bacteria: A retrospective analysis. *Antimicrob Agents Chemother* 2010; 54:1742–1748

90. Al-Hassan MN, Wilson JW, Lahr BD, et al: Beta-lactam and fluoroquinolone combination antibiotic therapy for bacteremia caused by gram-negative bacilli. *Antimicrob Agents Chemother* 2009; 53:1386–1394

91. Klastersky J: Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004; 39(Suppl 1):S32–S37

92. Martin-Loeches I, Lisboa T, Rodriguez A, et al: Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010; 36:612–620

93. Rodriguez A, Mendia A, Sirvent JM, et al: Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 2007; 35:1493–1498

94. Baddour LM, Yu VL, Klugman KP, et al: Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med* 2004; 170:440–444

95. Safdar N, Handelsman J, Maki DG: Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004; 4:519–527

96. Paul M, Silbiger I, Grozinsky S, et al: Beta lactam antibiotic monotherapy versus beta lactam aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2006; (1):CD003344

97. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al: Optimal management therapy for *Pseudomonas aeruginosa* ventilator associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med* 2007; 35:1888–1895

98. Jain S, Kamimoto L, Bramley AM, et al; 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team: Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009; 361:1935–1944

99. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza; Bautista E, Chotpitayasunondh T, Gao Z, et al: Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med* 2010; 362:1708–1719

100. Smith JR, Ariano RE, Toovey S: The use of antiviral agents for the management of severe influenza. *Crit Care Med* 2010; 38(Suppl 4):e43–e51

101. Fiore AE, Fry A, Shay D, et al; Centers for Disease Control and Prevention (CDC): Antiviral agents for the treatment and chemoprophylaxis of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; 60:1–24

102. Kalil A: A silent killer: Cytomegalovirus infection in the non-immunocompromised critically ill patient. *Crit Care Med* 2008; 36:3261–3264

103. Ziemann M, Sedemund-Adib B, Reibland P, et al: Increased mortality in long-term intensive care patients with active cytomegalovirus infection. *Crit Care Med* 2008; 36:3145–3150

104. Hotchkiss RS, Opal SM: Immunotherapy for sepsis: A new approach against an ancient foe. *N Engl J Med* 2010; 363:87–89

105. Miller GG, Dummer JS: Herpes simplex and varicella zoster viruses: Forgotten but not gone. *Am J Transplantation* 2007; 7:741–747

106. Jimenez MF, Marshall JC: Source control in the management of sepsis. *Intensive Care Med* 2001; 27:S49–S62

107. Moss RL, Musemeche CA, Kosloske AM: Necrotizing fascitis in children: Prompt recognition and aggressive therapy improve survival. *J Pediatr Surg* 1996; 31:1142–1146

108. Boyer A, Vargas F, Coste F, et al: Influence of surgical treatment on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med* 2009; 35:847–853

109. Bufalari A, Giustozzi G, Moggi L: Postoperative intraabdominal abscesses: Percutaneous versus surgical treatment. *Acta Chir Belg* 1996; 96:197–200

110. O'Grady NP, Alexander M, Dellinger EP, et al; Centers for Disease Control and Prevention: Guidelines for the prevention of intravascular catheter-related infections. *MMWR Recomm Rep* 2002; 51:1–29

111. O'Grady NP, Alexander M, Dellinger EP, et al: Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2002; 35:1281–1307

112. Mier J, Leon EL, Castillo A, et al: Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997; 173: 71–75

113. van Santvoort HC, Besselink MG, Bakker OJ, et al: A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; 362:1491–1502

114. Evans A, Winslow BH: Oxygen saturation and hemodynamic response in critically ill mechanically ventilated adults during intra hospital transport. *Am J Crit Care* 1995; 4:106–111

115. Aitken LM, Williams G, Harvey M, et al: Nursing considerations to complement the Surviving Sepsis Campaign. *Crit Care Med* 2011; 39:1800–1818

116. Liberati A, D'Amico R, Pifferi S, et al: Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *The Cochrane Collaboration* 2010; 9:1–72

117. de Jonge E, Schultz MJ, Spanjaard L, et al: Effects of selective decontamination of the digestive tract on mortality and acquisition of resistance bacteria on intensive care: A randomised controlled trial. *Lancet* 2003; 362:1011–1016

118. de Smet AMGA, Kluytmans JAJM, Cooper BS, et al: Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; 360:20–31

119. Cuthbertson BH, Francis J, Campbell MK, et al, for the SuDDICU Study Groups. A study of the perceived risks, benefits and barriers to the use of SDD in adult critical care units (SuDDICU study). *Trials* 2010; 11:117

120. de Smet AMGA, Kluytmans JAJM, Blok HEM, et al: Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in the intensive care unit: An open label, cluster grouped, randomized cross over study. *Lancet Infect Dis* 2011; 11:372–380

121. Oostdijk EAN, de Smet AMGA, Blok HEM, et al: Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med* 2010; 181:452–457

122. Ochoa-Ardila ME, García-Cañas A, Gómez-Mediavilla K, et al: Long-term use of selective decontamination of the digestive tract does not increase antibiotic resistance: A 5-year prospective cohort study. *Intensive Care Med* 2011; 37:1458–1465

123. Guidet B, Martinet O, Boulain T, et al: Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care* 2012; 16:R94

124. Perner A, Haase N, Guttormsen AB, et al, for the 6S Trial Group and the Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124–134

125. Myburgh JA, Finfer S, Bellomo R, et al, for the CHEST Investigators and the Autralian and New Zealand Intensive Care Society Critical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; DOI: 10.1056/NEJMoa1209759

126. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2011; (3):CD000567. Review

127. Schortgen F, Lacherade JC, Bruneel F, et al: Effects of hydroxyethyl starch and gelatin on renal function in severe sepsis: A multicentre randomised study. *Lancet* 2001; 357: 911–916

128. McIntyre LA, Fergusson D, Cook DJ, et al: Fluid resuscitation in the management of early septic shock (FINESS): A randomized controlled feasibility trial. *Can J Anaesth* 2008; 55:819–826

129. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139

130. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256

131. Delaney AP, Dan A, McCaffrey J, Finfer S: The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. *Crit Care Med* 2011; 39:386–391

132. Marik PE, Teboul JL: Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2011; 1:1

133. Marik PE, Cavallazzi R, Vasu T, Hirani A: Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Crit Care Med* 2009; 37:2642–2647

134. Hollenberg SM, Ahrens TS, Annane D, et al: Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; 32:1928–1948

135. LeDoux D, Astiz ME, Carpati CM, et al: Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 2000; 28:2729–2732

136. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831

137. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758–2765

138. De Backer D, Creteur J, Silva E, et al: Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659–1667

139. Day NP, Phu NH, Bethell DP, et al: The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; 348:219–223

140. Le Tulzo Y, Seguin P, Gacouin A, et al: Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: A preliminary descriptive study. *Intensive Care Med* 1997; 23:664–670

141. Bollaert PE, Bauer P, Audibert G, et al: Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock. *Chest* 1990; 98:949–953

142. Zhou SX, Qiu HB, Huang YZ, et al: Effects of norepinephrine, epinephrine, and norepinephrine-dobutamine on systemic and gastric mucosal oxygenation in septic shock. *Acta Pharm Sin* 2002; 23:654–658

143. Levy B, Bollaert PE, Charpentier C, et al: Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: A prospective, randomized study. *Intensive Care Med* 1997; 23:282–287

144. Mackenzie SJ, Kapadia F, Nimmo GR, et al: Adrenaline in treatment of septic shock: Effects on haemodynamics and oxygen transport. *Intensive Care Med* 1991; 17:36–39

145. Moran JL, O'Fathartaigh MS, Peisach AR, et al: Epinephrine as an inotropic agent in septic shock: A dose-profile analysis. *Crit Care Med* 1993; 21:70–77

146. Yamazaki T, Shimada Y, Taenaka N, et al: Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. *Crit Care Med* 1982; 10:432–435

147. Gregory JS, Bonfiglio MF, Dasta JF, et al: Experience with phenylephrine as a component of the pharmacologic support of septic shock. *Crit Care Med* 1991; 19:1395–1400

148. Annane D, Vignon P, Renault A, et al, for the CATS Study Group: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomized trial. *Lancet* 2007; 370:676–684

149. Regnier B, Rapin M, Gory G, et al: Haemodynamic effects of dopamine in septic shock. *Intensive Care Med* 1977; 3:47–53

150. Ruokonen E, Takala J, Kari A, et al: Regional blood flow and oxygen transport in septic shock. *Crit Care Med* 1993; 21:1296–1303

151. Marik PE, Mohedin M: The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994; 272:1354–1357

152. Patel GP, Grahe JS, Sperry M, et al: Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock* 2010; 33:375–380

153. De Backer D, Biston P, Devriendt J, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779–789

154. De Backer D, Aldecoa C, Njimi H, Vincent JL: Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. *Crit Care* 2012; 40:725‒730

155. Seguin P, Bellissant E, Le-Tulzo Y, et al: Effects of epinephrine compared with the combination of dobutamine and norepinephrine on gastric perfusion in septic shock. *Clin Pharmacol Ther* 2002; 71:381–388

156. Myburgh JA, Higgins A, Jovanovska A, et al; CAT Study Investigators: A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34:2226–2234

157. Morelli A, Ertmer C, Rehberg S, et al: Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: A randomized, controlled trial. *Crit Care* 2008; 12:R143

158. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95:1122–1125

159. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582

160. Dünser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock: A prospective, randomized, controlled study. *Circulation* 2003; 107:2313–2319

161. Holmes CL, Patel BM, Russell JA, et al: Physiology of vasopressin relevant to management of septic shock. *Chest* 2001; 120:989–1002

162. Malay MB, Ashton RC, Landry DW, et al: Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699–705

163. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416–1421

164. Lauzier F, Levy B, Lamarre P, et al: Vasopressin or norepinephrine in early hyperdynamic septic shock: A randomized clinical trial. *Intensive Care Med* 2006; 32:1782–1789

165. O'Brien A, Calpp L, Singer M: Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; 359:1209–1210

166. Sharshar T, Blanchard A, Paillard M, et al: Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752–1758

167. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887

168. Dünser MW, Mayr AJ, Tura A, et al: Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: Incidence and risk factors. *Crit Care Med* 2003; 31:1394–1398

169. Albanèse J, Leone M, Delmas A, Martin C: Terlipressin or norepinephrine in hyperdynamic septic shock: A prospective, randomized study. *Crit Care Med* 2005; 33:1897–1902

170. Morelli A, Ertmer C, Lange M, et al: Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: The DOBUPRESS study. *Br J Anesth* 2008; 100:494–503

171. Morelli A, Ertmer C, Rehberg S, et al: Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): A randomized, controlled pilot study. *Crit Care* 2009; 13:R130

172. Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356:2139–2143

173. Kellum J, Decker J: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001; 29:1526–1531

174. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995; 333:1025–1032

175. Hayes MA, Timmins AC, Yau EHS, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722

176. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871

177. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732

178. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650

179. Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124

180. Annane D, Bellissant E, Bollaert PE, et al: Corticosteroids in the treatment of severe sepsis and septic shock in adults: A systematic review. *JAMA* 2009; 301:2362–2375

181. Sligl WI, Milner DA Jr, Sundar S, et al: Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. *Clin Infect Dis* 2009; 49:93–101

182. Patel GP, Balk RA: Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med* 2012; 185:133–139

183. Oppert M, Schindler R, Husung C, et al: Low dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med* 2005; 33:2457–2464

184. Yildiz O, Doganay M, Aygen B, et al: Physiologic-dose steroid therapy in sepsis. *Crit Care* 2002; 6:251–259

185. Briegel J, Möhnle P, Sprung CL, et al, for the CORTICUS Study Group: Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. *Intensive Care Med* 2009; 35:2151–2156

186. Allolio B, Dorr H, Stuttmann R, et al: Effect of a single bolus of etomidate upon eight major corticosteroid hormone and plasma ACTH. *Clin Endocrinol (Oxf)* 1985; 22:281–286

187. Jabre P, Combes X, Lapostolle F, et al: Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 2009; 374:293–300

188. Cuthbertson BH, Sprung CL, Annane D, et al: The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med* 2009; 35:1868–1876

189. Keh D, Boehnke T, Weber-Carstens S, et al: Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: A double-blind, randomized, placebo controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520

190. Huh JW, Choi HS, Lim CM, et al: Low-dose hydrocortisone treatment for patients with septic shock: A pilot study comparing 3 days with 7 days. *Respirology* 2011; 16:1088–1095

191. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248

192. Meijvis SCA, Hardemann H, Remmelts HHF, et al: Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: A randomized, double-blind, placebo-controlled trial. *Lancet* 2011; 377:2023–2030

193. Weber-Carstens S, Deja M, Bercker S, et al: Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Med* 2007; 33:730–733

194. Hébert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion in critical care. *N Engl J Med* 1999; 340:409–417

195. Hajjar LA, Vincent JL, Galas FRBG, et al: Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. *JAMA* 2010; 304:1559–1567

196. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3029

197. Lorente JA, Landín L, dePablo R, et al: Effects of blood transfusion on oxygen transport variables in severe sepsis. *Crit Care Med* 1993; 21:1312–1318

198. Fernandes CJ, Akamine N, DeMarco FVC, et al: Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001; 5:362–567

199. Corwin HL, Gettinger A, Rodriguez RM, et al: Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized double-blind, placebo-controlled trial. *Crit Care Med* 1999; 27:2346–2350

200. Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA* 2002; 28:2827–2835

201. College of American Pathologists: Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; 271:777–781

202. Canadian Medical Association Expert Working Group: Guidelines for red blood cell and plasma transfusion for adults and children. *Can Med Assoc J* 1997; 156:S1–S24

203. American Society of Anaesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy. *Anesthesiology* 1996; 84:732–747

204. Liumbruno GL, Bennardello F, Lattanzio A, et al: Recommendations for the transfusion of plasma and platelets. *Blood Transfus* 2009; 7:132–150

205. Abdel-Wahab OI, Healy B, Dzik WH: Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion* 2006; 46:1279–1285

206. Stanworth SJ, Walsh TS, Prescott RJ, et al: A national study of plasma use in critical care: Clinical indications, dose, and effect on prothrombin time. *Crit Care* 2011; 15:R108

207. Warren BL, Eid A, Singer P, et al: High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA* 2001; 286:1869–1878

208. Wiedermann CJ, Hoffmann JN, Juers M, et al: High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: Efficacy and safety. *Crit Care Med* 2006; 34:285–292

209. Schiffer CA, Anderson KC, Bennett CL, et al: Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19:1519–1538

210. Guidelines for the use of platelet transfusions. *Br J Haematol* 2003; 122:10–23

211. Werdan K, Pilz G, Bujdoso O, et al: Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study. *Crit Care Med* 2007; 35:2693–2701

212. INIS Collaborative Group; Brocklehurst P, Farrell B, King A, et al: Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med* 2011; 365:1201–1211

213. Alejandria MM, Lansang MAD, Dans LF, Mantaring JB III: Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database Syst Rev* 2002; (1):CD001090

214. Burns ER, Lee V, Rubinstein A: Treatment of septic thrombocytemia with immune globulin. *J Clin Immunol* 1991; 11:363–368

215. Darenberg J, Ihendyane N, Sjölin J, et al: Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003; 37:333–340

216. Hentrich M, Fehnle K, Ostermann H, et al: IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: A randomized, controlled, multiple-center trial. *Crit Care Med* 2006; 34:1319–1325

217. Rodriguez A, Rello J, Neira J, et al: Effects of high-dose intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. *Shock* 2005; 23:298–304

218. Pildal J, Gøtzsche PC: Polyclonal immunoglobulin for treatment of bacterial sepsis: A systematic review. *Clin Infect Dis* 2004; 39:38–46

219. Laupland KB, Kirkpatrick AW, Delaney A: Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis. *Crit Care Med* 2007; 35:2686–2692

220. Kreymann KG, de Heer G, Nierhaus A, Kluge S: Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007; 35:2677–2685

221. Turgeon AF, Hutton B, Fergusson DA, et al: Meta-analysis: Intravenous immunoglobulin in critically ill adult patients with sepsis. *Ann Intern Med* 2007; 146:193–203

222. Angstwurm MW, Engelmann L, Zimmermann T, et al: Selenium in intensive care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007; 35:118–126

223. Forceville X, Laviolle B, Annane D, et al: Effects of high doses of selenium, a sodium selenite, in septic shock: A placebo-controlled, randomized, double-blind, phase II study. *Crit Care* 2007; 11:R73

224. Manzanares W, Biestro A, Torre MH, et al: High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation. *Intensive Care Med* 2011; 37:1120–1127

225. Berger MM, Eggimann P, Heyland DK, et al: Reduction of nosocomial pneumonia after major burns by trace element supplementation: Aggregation of two randomized trials. *Crit Care* 2006; 10:R153

226. Mishra V, Baines M, Perry SE, et al: Effect of selenium supplementation on biochemical markers and outcome in critically ill patients. *Clin Nutr* 2007; 26:41–50

227. Andrews PJ, Avenell A, Noble DW, et al: Randomised trial of glutamine, selenium, or both, to supplemental parenteral nutrition for critically ill patients. *BMJ* 2011; 342:d1542

228. Wang Z, Forceville X, Van Antwerpen P, et al: A large-bolus injection, but not continuous infusion of sodium selenite improves outcome in peritonitis. *Shock* 2009; 32:140–146

229. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709

230. Abraham E, Laterre P-F, Garg F, et al, for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; 353:1332–1341

231. Nadel S, Goldstein B, Williams MD, et al; REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) Study Group: Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial *Lancet* 2007; 369:836–843

232. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm277212.htm. Accessed December 18, 2011.

233. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med 1994*; 149:818–824

234. Ranieri VM, Rubenfeld GD, Thompson BT, et al: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:25226–25233

235. 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

236. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354

237. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome: The multicenter trail group on tidal volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831–1838

238. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27:1492–1498

239. Stewart TE, Meade MO, Cook DJ, et al: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355–361

240. Eichacker PQ, Gerstenberger EP, Banks SM, et al: Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. *Am J Respir Crit Care Med* 2002; 166:1510–1514

241. Putensen C, Theuerkauf N, Zinserling J, et al: Meta-analysis: Ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med* 2009; 151:566–576

242. Burns KE, Adhikari NK, Slutsky AS, et al: Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury: A systematic review and meta-analysis. *PLoS One* 2011; 6:e14623

243. Tobin MJ: Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1360–1361

244. Marini JJ, Gattinoni L: Ventilatory management of acute respiratory distress syndrome: A consensus of two. *Crit Care Med* 2004; 32:250–255

245. Hager DN, Krishnan JA, Hayden DL, et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245

246. Checkley W, Brower R, Korpak A, et al: Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med* 2008; 177:1215–1222

247. Kallet RH, Jasmer RM, Luce JM, et al: The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). *Am J Respir Crit Care Med* 2000; 161:1149–1153

248. Weber T, Tschernich H, Sitzwohl C, et al: Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; 162:1361–1365

249. Determann RM, Royakkers A, Wolthuis EK, et al: Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: A preventive randomized controlled trial. *Crit Care* 2010; 14:R1

250. Yilmaz M, Keegan MT, Iscimen R, et al: Toward the prevention of acute lung injury: Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med* 2007; 35:1660–1666

251. Gajic O, Dara SI, Mendez JL, et al: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32:1817–1824

252. Schultz MJ: Lung-protective mechanical ventilation with lower tidal volumes in patients not suffering from acute lung injury: A review of clinical studies. *Med Sci Monit* 2008; 14:RA22–RA26

253. Marini JJ, Ravenscraft SA: Mean airway pressure: Physiologic determinants and clinical importance—part 1: Physiologic determinants and measurements. *Crit Care Med* 1992; 20:1461–1472

254. Gattinoni L, Marcolin R, Caspani ML, et al: Constant mean airway pressure with different patterns of positive pressure breathing during the adult respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1985; 21:275–279

255. Pesenti A, Marcolin R, Prato P, et al: Mean airway pressure vs. positive end-expiratory pressure during mechanical ventilation. *Crit Care Med* 1985; 13:34–37

256. Mercat A, Richard JC, Vielle B, et al: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655

257. Meade MO, Cook DJ, Guyatt GH, et al: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645

258. Brower RG, Lanken PN, MacIntyre N, et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336

259. Briel M, Meade M, Mercat A, et al: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010; 303:865–873

260. Amato MB, Barbas CS, Medeiros DM, et al: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995; 152:1835–1846

261. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–1786

262. Pipeling MR, Fan E: Therapies for refractory hypoxemia in acute respiratory distress syndrome. *JAMA* 2010; 304:2521–2527

263. Fan E, Wilcox ME, Brower RG, et al: Recruitment maneuvers for acute lung injury: A systematic review. *Am J Respir Crit Care Med* 2008; 178:1156–1163

264. Stocker R, Neff T, Stein S, et al: Prone positioning and low-volume pressure-limited ventilation improve survival in patients with severe ARDS. *Chest* 1997; 111:1008–1017

265. Lamm WJ, Graham MM, Albert RK: Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994; 150:184–193

266. Jolliet P, Bulpa P, Chevrolet JC: Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med* 1998; 26:1977–1985

267. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 2004; 292:2379–2387

268. Taccone P, Pesenti A, Latini R, et al: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977–1984

269. Mancebo J, Fernandez R, Blanch L, et al: A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:1233–1239

270. Gattinoni L, Tognoni G, Pesenti A, et al: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573

271. Sud S, Friedrich JO, Taccone P, et al: Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. *Intensive Care Med* 2010; 36:585–599

272. Sud S, Sud M, Friedrich JO, et al: High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): Systematic review and meta-analysis. *BMJ* 2010; 340:c2327

273. Noah MA, Peek GJ, Finney SJ, et al: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). *JAMA* 2011; 306:1659–1668

274. Checkley W: Extracorporeal membrane oxygenation as a first-line treatment strategy for ARDS: Is the evidence sufficiently strong? *JAMA* 2011; 306:1703–1704

275. Peek GJ, Mugford M, Tiruvoipati R, et al: Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicenter randomised controlled trial. *Lancet* 2009; 374:1330

276. Adhaikari NK, Burns KE, Friedrich JO: Effect of nitric oxide on oxygenation and mortality in acute lung injury: Systematic review and meta-analysis. *BMJ* 2007; 334:779

277. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999; 354:1851–1858

278. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al: Feasibility and effects of the semi-recumbent position to prevent ventilator-associated pneumonia: A randomized study. *Crit Care Med* 2006; 34:396–402

279. Antonelli M, Conti G, Rocco M, et al: A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; 339:429–435

280. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168:1438–1444

281. Rana S, Jenad H, Gay PC, et al: Failure of non-invasive ventilation in patients with acute lung injury: Observational cohort study. *Crit Care* 2006; 10:R79

282. Domenighetti G, Moccia A, Gayer R: Observational case-control study of non-invasive ventilation in patients with ARDS. *Monaldi Arch Chest Dis* 2008; 69:5–10

283. Ely W, Baker AB, Dunagen DP: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *New Engl J Med* 1996; 335:1865–1869

284. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342:1471–1477

285. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): A randomised controlled trial. *Lancet* 2008; 371:126–134

286. Iberti TJ, Fischer EP, Leibowitz AB, et al; Pulmonary Artery Catheter Study Group: A multicenter study of physicians' knowledge of the pulmonary artery catheter. *JAMA* 1990; 264:2928–2932

287. Al-Kharrat T, Zarich S, Amoateng-Adjepong Y, et al: Analysis of observer variability in measurement of pulmonary artery occlusion pressures. *Am J Respir Crit Care Med* 1999; 160:415–420

288. Connors AF Jr, McCaffree DR, Gray BA: Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med* 1983; 308:263–267

289. Osman D, Ridel C, Ray P, et al: Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; 35:64–68

290. Richard C, Warszawski J, Anguel N, et al: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290:2713–2720

291. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wheeler AP, Bernard GR, Thompson BT, et al: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224

292. Sandham JD, Hull RD, Brant RF, et al: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14

293. Shah MR, Hasselblad V, Stevenson LW, et al: Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 2005; 294:1664–1670

294. Harvey S, Harrison DA, Singer M, et al: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-man): A randomised controlled trial. *Lancet* 2005; 366:472–477

295. Harvey S, Young D, Brampton W, et al: Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev* 2006; (3):CD003408

296. Sibbald WJ, Short AK, Warshawski FJ, et al: Thermal dye measurements of extravascular lung water in critically ill patients: Intravascular starling forces and extravascular lung water in the adult respiratory distress syndrome. *Chest* 1985; 87:585–592

297. Martin GS, Mangialardi RJ, Wheeler AP, et al: Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2002; 30:2175–2182

298. Mitchell JP, Schuller D, Calandrino FS, et al: Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; 145:990–998

299. Schuller D, Mitchell JP, Calandrino FS, et al: Fluid balance during pulmonary edema: Is fluid gain a marker or a cause of poor outcome? *Chest* 1991; 100:1068–1075

300. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575

301. Perkins GD, McAuley DF, Thickett DR, Gao F: The β-agonist lung injury trial (BALTI): A randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med* 2006; 173:281–287

302. Matthay MA, Brower RG, Carson S, et al: Randomized, placebo-controlled clinical trial of an aerolosolized β-2 agonist for treatment of acute lung injury. *Am J Resp Crit Care Med* 2011; 184:561–568

303. Gao Smith F, Perkins DG, Gates S, et al; BALTI-2 study investigators: Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): A multicentre, randomised controlled trial. *Lancet* 2012; 379:229–235

304. Marx WH, DeMaintenon NL, Mooney KF, et al: Cost reduction and outcome improvement in the intensive care unit. *J Trauma* 1999; 46:625–629; discussion 629–630

305. MacLaren R, Plamondon JM, Ramsay KB, et al: A prospective evaluation of empiric versus protocol-based sedation and analgesia. *Pharmacotherapy* 2000; 20:662–672

306. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615

307. Strom T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. *Lancet* 2010; 375:475–480

308. Riker RR, Shehabi Y, Bokesch PM, et al: Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489–499

309. Tan JA, Ho KM: Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: A meta-analysis. *Intensive Care Med* 2010; 36:926–939

310. Devlin JW, Boleski G, Mlynarek M, et al: Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999; 27:1271–1275

311. De Jonghe B, Cook D, Sharshar T, et al; Groupe de réflexion et d'étude sur les neuromyopathies en réanimation: Acquired neuromuscular disorders in critically ill patients: A systematic review. *Intensive Care Med* 1998; 24:1242–1250

312. Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; 114:541–548

313. Kress JP, Vinayak AG, Levitt J, et al: Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* 2007; 35:365–371

314. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. *Lancet* 2009; 373:1874–1882

315. Klessig HT, Geiger HJ, Murray MJ, et al: A national survey on the practice patterns of anesthesiologist intensivists in the use of muscle relaxants. *Crit Care Med* 1992; 20:1341–1345

316. Murray MJ, Cowen J, DeBlock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2002; 30:142–156

317. Hansen-Flaschen JH, Brazinsky S, Basile C, et al: Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure: A national survey. *JAMA* 1991; 266:2870–2875

318. Freebairn RC, Derrick J, Gomersall CD, et al: Oxygen delivery, oxygen consumption, and gastric intramucosal pH are not improved by a computer-controlled, closed-loop, vecuronium infusion in severe sepsis and septic shock. *Crit Care Med* 1997; 25:72–77

319. Papazian L, Forel JM, Gacouin A, et al: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116

320. Forel JM, Roch A, Marin V, et al: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2749–2757

321. Shapiro BA, Warren J, Egol AB, et al: Society of Critical Care Medicine: Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: An executive summary. *Crit Care Med* 1995; 23:1601–1605

322. Meyer KC, Prielipp RC, Grossman JE, et al: Prolonged weakness after infusion of atracurium in two intensive care unit patients. *Anesth Analg* 1994; 78:772–774

323. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weakness in the intensive care unit: A study of ninety-two patients. *Muscle Nerve* 1998; 21:610–617

324. Rudis MI, Sikora CA, Angus E, et al: A prospective, randomized, controlled evaluation of peripheral nerve stimulation versus standard clinical dosing of neuromuscular blocking agents in critically ill patients. *Crit Care Med* 1997; 25:575–583

325. Frankel H, Jeng J, Tilly E, et al: The impact of implementation of neuromuscular blockade monitoring standards in a surgical intensive care unit. *Am Surg* 1996; 62:503–506

326. Strange C, Vaughan L, Franklin C, et al: Comparison of train-of-four and best clinical assessment during continuous paralysis. *Am J Respir Crit Care Med* 1997; 156:1556–1561

327. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367

328. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461

329. Arabi YM, Dabbagh OC, Tamim HM: Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 2008; 36:3190–3197

330. De La Rosa GDC, Hernando Donado J, Restrepo AH: Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: A randomised clinical trial. *Critical Care* 2008; 12:R120

331. COIITSS Study Investigators; Annane D, Cariou A, Maxime V, et al: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. *JAMA* 2012; 303:341–348

332. The NICE-SUGAR Study Investigators: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360:1283–1297

333. Preiser JC, Devos P, Ruiz-Santana S: A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: The Glucontrol study. *Intensive Care Med* 2009; 35:1738–1748

334. Wiener RS, Wiener DC, Larson RJ: Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. *JAMA* 2008; 300:933–936

335. Griesdale DEG, de Souza RJ, van Dam RM, et al: Intensive insulin therapy and mortality among critically ill patients: A meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; 180:821–827

336. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: A systematic review and metaanalysis. *Chest* 2010; 137:544–551

337. Friedrich JO, Chant C, Adhikari NKJ: Does intensive insulin therapy really reduce mortality in critically ill surgical patients? A reanalysis of meta-analytic data. *Critical Care* 2010; 14:324–330

338. Kansagara D, Fu R, Freeman M, et al: Intensive insulin therapy in hospitalized patients: A systematic review. *Ann Intern Med* 2011; 154:268–282

339. Peberdy MA, Callaway CW, Neumar RW, et al: Part 9: Post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122:S768–S786

340. Qaseem A, Humphrey LL, Chou R, et al: Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011; 154:260–267

341. Moghissi ES, Korytkowski MT, Dinardo M, et al: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32:1119–1131

342. Jacobi J, Bircher N, Krinsley J, et al: Guidelines for the use of insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med*; in press

343. Kauffmann RM, Hayes RM, Jenkins JM, et al: Provision of balanced nutrition protects against hypoglycemia in the critically ill surgical patient. *JPEN J Parenter Enteral Nutr* 2011; 35:686–694

344. Egi M, Bellomo R, Stachowski E, et al: Variability in blood glucose concentrations and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105:233–234

345. Krinsley JS: Glycemic variability: A strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36:3008–3013

346. Mackenzie IMJ, Whitehouse T, Nightingale PG: The metrics of glycaemic control in critical care. *Intensive Care Med* 2011; 37:435–443

347. Egi M, Bellomo R, Stachowski E: Blood glucose concentration and outcome of critical illness: The impact of diabetes. *Crit Care Med* 2008; 36:2249–2255

348. Krinsley JS: Glycemic variability and mortality in critically ill patients: The impact of diabetes. *J Diabetes Sci Technol* 2009; 3:1292–1301

349. Nichols JH: Bedside testing, glucose monitoring, and diabetes management. *In:* Principles of Point of Care Testing. Kost GJ (Ed). Philadelphia, Lippincott Williams & Wilkins, 2002

350. Kanji S, Buffie J, Hutton B, et al: Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005; 33:2778–2785

351. Hoedemaekers CW, Klein Gunnewiek JM, Prinsen MA, et al: Accuracy of bedside glucose measurement from three glucometers in critically ill patients. *Crit Care Med* 2008; 36:3062–3066

352. Khan AI, Vasquez Y, Gray J, et al: The variability of results between point-of-care testing glucose meters and the central laboratory analyzer. *Arch Pathol Lab Med* 2006; 130:1527–1532

353. Desachy A, Vuagnat AC, Ghazali AD, et al: Accuracy of bedside glucometry in critically ill patients: Influence of clinical characteristics and perfusion index. *Mayo Clin Proc* 2008; 83:400–405

354. Fekih Hassen M, Ayed S, Gharbi R, et al: Bedside capillary blood glucose measurements in critically ill patients: Influence of catecholamine therapy. *Diabetes Res Clin Pract* 2010; 87:87–91

355. Wilson M, Weinreb J, Soo Hoo GW: Intensive insulin therapy in critical care: A review of a dozen protocols. *Diabetes Care* 2007; 30:1005–1011

356. Newton CA, Smiley D, Bode BW, et al: A comparison study of continuous insulin infusion protocols in the medical intensive care unit: Computer-guided vs. standard column-based algorithms. *J Hosp Med* 2010; 5:432–437

357. Dortch MJ, Mowery NT, Ozdas A, et al: A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *JPEN J Parenter Enteral Nutr* 2008; 32:18–27

358. Mauritz W, Sporn P, Schindler I, et al: Acute renal failure in abdominal infection: Comparison of hemodialysis and continuous arteriovenous and continuous hemofiltration. *Anasth Intensivther Nortfallmed* 1986; 21:212–217

359. Bartlett RH, Mault JR, Dechert RE, et al: Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure. *Surgery* 1986; 100:400–408

360. Kierdorf H: Continuous versus intermittent treatment: Clinical results in acute renal failure. *Contrib Nephrol* 1991; 93:1–12

361. Bellomo R, Mansfield D, Rumble S, et al: Acute renal failure in critical illness: Conventional dialysis versus continuous hemodiafiltration. *Am Soc Artif Intern Organs J* 1992; 38:M654–M657

362. Bellomo R, Farmer M, Parkin G, et al: Severe acute renal failure: A comparison of acute continuous hemodiafiltration and conventional dialytic therapy. *Nephron* 1995; 71:59–64

363. Kruczinski K, Irvine-Bird K, Toffelmire EB, et al: A comparison of continuous arteriovenous hemofiltration and intermittent hemodialysis in acute renal failure patients in intensive care unit. *Am Soc Artif Intern Organs J* 1993; 38:M778–M781

364. Van Bommel EH, Bouvy ND, Sob KL, et al: Acute dialytic support for the critically ill: Intermittent hemodialysis versus continuous arteriovenous hemodiafiltration. *Am J Nephrol* 1995; 15:192–200

365. Guerin C, Girard R, Selli JM, et al: Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: Results from a multicenter prospective epidemiological survey. *Intensive Care Med* 2002; 28:1411–1418

366. Kellum JA, Angus DC, Johnson JP, et al: Continuous versus intermittent renal replacement therapy: A meta-analysis. *Intensive Care Med* 2002; 28:29–37

367. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the intensive care unit: A systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; 40:875–885

368. Mehta RL, McDonald B, Gabbai FB, et al: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163

369. Gasparovic V, Filipovic-Greie I, Merkler M, et al: Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)—What is the procedure of choice in critically ill patients? *Ren Fail* 2003; 25:855–862

370. Augustine JJ, Sandy D, Seifert TH, et al: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004; 44:1000–1007

371. Uehlinger DE, Jakob SM, Ferrari P, et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20:1630–1637

372. Vinsonneau C, Camus C, Combes A, et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 2006; 368:379–85

373. John S, Griesbach D, Baumgärtel M, et al: Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: A prospective, randomized clinical trial. *Nephrol Dial Transplant* 2001; 16:320–327

374. Misset B, Timsit JF, Chevret S, et al: A randomized cross-over comparison of the hemodynamic response to intermittent hemodialysis and continuous hemofiltration in ICU patients with acute renal failure. *Intensive Care Med* 1996; 22:742–746

375. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous venovenous haemofiltration on outcomes of acute renal failure: A prospective randomized trial. *Lancet* 2000; 356:26–30

376. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 2002; 30:2205–2211

377. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; 346:305–310

378. Saudan P, Niederberger M, De Seigneux S, et al: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006; 70:1312–1317

379. Cooper DJ, Walley KR, Wiggs BR, et al: Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis: A prospective, controlled clinical study. *Ann Intern Med* 1990; 112:492–498

380. Mathieu D, Neviere R, Billard V, et al: Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study. *Crit Care Med* 1991; 19:1352–1356

381. Cade JF: High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982; 10:448–450

382. Halkin H, Goldberg J, Modal M, et al: Reduction in mortality in general medical in-patients by low-dose heparin prophylaxis. *Ann Intern Med* 1982; 96:561–565

383. Pingleton SK, Bone RC, Pingleton WW, et al: Prevention of pulmonary emboli in a respiratory intensive care unit. *Chest* 1981; 79:647–650

384. Belch JJ, Lowe DO, Ward AG, et al: Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 1981; 26:115–117

385. Gardlund B: Randomized, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases: The Heparin Prophylaxis Study Group. *Lancet* 1996; 347:1357–1361

386. Samama MM, Cohen AT, Darmon JY, et al: A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; 341:793–800

387. Dahan R, Houlbert D, Caulin C, et al: Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: A randomized double-blind trial. *Haemostasis* 1986; 16:159–164

388. Hirsch DR, Ingenito EP, Goldhaber SZ: Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA* 1995; 274:335–337

389. Fraisse F, Holzapfel L, Couland JM, et al: Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD: The Association of Non-University Affiliated

Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med* 2000; 161:1109–1114

390. Kupfer Y, Anwar J, Seneviratne C, et al: Prophylaxis with subcutaneous heparin significantly reduces the incidence of deep venous thrombophlebitis in the critically ill. Abstr. *Am J Crit Care Med* 1999; 159(Suppl):A519

391. Geerts W, Cook D, Shelby R, et al: Venous thromboembolism and its prevention in critical care. *J Crit Care* 2002; 17:95–104

392. Attia J, Ray JG, Cook DJ, et al: Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001; 161:1268–1279

393. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Cook D, Meade M, Guyatt G, et al: Dalteparin versus unfractionated heparin in critically ill patients. *New Engl J Med* 2011; 364:1305–1314

394. King CS, Holley AB, Jackson JF, et al: Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A meta-analysis. *Chest* 2007; 131:507–516

395. Douketis J, Cook D, Meade M, et al (the Canadian Critical Care Trials Group): Prophylaxis against deep vein thrombosis in critically ill patients with severe renal insufficiency with the low-molecular-weight heparin dalteparin: An assessment of safety and pharmacodynamics: The DIRECT study. *Arch Intern Med* 2008; 168:1805–1812

396. Vanek VW: Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg* 1998; 64:1050–1058

397. Turpie AG, Hirsh J, Gent M, et al: Prevention of deep vein thrombosis in potential neurosurgical patients: A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 1989; 149:679–681

398. Agu O, Hamilton G, Baker D: Graduated compression stocking in the prevention of venous thromboembolism. *Br J Surg* 1999; 86:992–1004

399. Kakkos SK, Caprini JA, Geroulakos G, et al: Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. *Cochrane Database Syst Rev* 2008; (4):CD005258

400. German Hip Arthroplasty Trial Group (GHAT): Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement: A randomized trial. *Arch Orthop Trauma Surg* 1992; 111:110–120

401. Colwell CW, Spiro TE, Trowbridge AA, et al: Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement: A clinical trial comparing efficacy and safety. *J Bone Joint Surg Am* 1994; 76:3–14

402. Geerts WH, Jay RM, Code KI, et al: A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335:701–707

403. Guyatt GH, Akl EA, Crowther M, David, et al: Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(Suppl 2):7S-47S

404. Basso N, Bagarani M, Materia A, et al: Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high risk patients. *Am J Surg* 1981; 141:339–342

405. Bresalier RS, Grendell JH, Cello JP, et al: Sucralfate versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients. *Am J Med* 1987; 83:110–116

406. Poleski MH, Spanier AH: Cimetidine versus antacids in the prevention of stress erosions in critically ill patients. *Am J Gastroenterol* 1986; 81:107–111

407. Stothert JC, Simonowitz DA, Dellinger EP, et al: Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. *Ann Surg* 1980; 192:169–174

408. Cook DJ, Fuller HD, Guyatt GH, et al: Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330:377–381

409. Schuster DP, Rowley H, Feinstein S, et al: Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. *Am J Med* 1984; 76:623–629

410. Kahn JM, Doctor JN, Rubenfeld GD: Stress ulcer prophylaxis in mechanically ventilated patients: Integrating evidence and judgment using a decision analysis. *Intensive Care Med* 2006; 32:1151–1158

411. Cook DJ, Reeve BK, Guyatt GH, et al: Stress ulcer prophylaxis in critically ill patients: Resolving discordant meta-analyses. *JAMA* 1996; 275:308–314

412. Marik P, Vasu T, Hirani A, Pachinburavan M:. Stress ulcer prophylaxis in the new millennium: A systematic review and meta-analysis. *Crit Care Med* 2010; 38:222-228

413. Howell MD, Novack C, Grgurich P, et al: Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med* 2010; 170:784-790

414. Leonard J, Marshall JK, Moayyedi P: Systematic review of the risk of enteric infection in patients taking acid supression. *Am J Gastroenterol* 2007; 102: 2047-2056

415. Cook D, Guyatt G, Marshall J, et al: A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; 338:791–797

416. Lin, Pei-Chin M. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: A meta-analysis. *Crit Care Med* 2010; 38:1197-1205

417. Pongprasobchai S, Kridkratoke S, Nopmaneejumruslers C:. Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: a meta-analysis. *J Med Assoc Thai* 2009: 92:632-637

418. Alhazzani W, Alshahrani M, Moayyedi P, Jaeschke R. Stress ulcer prophylaxis in critically ill patients: review of the evidence. Pol Arch Med Wewn 2012; 122:107-114

419. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: A prospective, randomized study. *J Trauma* 1986; 26:874–881

420. Chiarelli A, Enzi G, Casadei A, et al: Very early nutrition supplementation in burned patients. *Am J Clin Nutr* 1990; 51:1035–1039

421. Eyer SD, Micon LT, Konstantinides FN, et al: Early enteral feeding does not attenuate metabolic response after blunt trauma. *J Trauma* 1993; 34:639–643

422. Chuntrasakul C, Siltharm S, Chinswangwatanakul V, et al: Early nutritional support in severe traumatic patients. *J Med Assoc Thai* 1996; 79:21–26

423. Singh G, Ram RP, Khanna SK: Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg* 1998; 187:142–146

424. Kompan L, Kremzar B, Gadzijev E, et al: Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. *Intensive Care Med* 1999; 25:157–161

425. Minard G, Kudsk KA, Melton S, et al: Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN J Parenter Enteral Nutr* 2000; 24:145–149

426. Pupelis G, Selga G, Austrums E, et al: Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition* 2001; 17:91–94

427. Kompan L, Vidmar G, Spindler-Vesel A, et al: Is early enteral nutrition a risk factor for gastric intolerance and pneumonia? *Clin Nutr* 2004; 23:527–532

428. Nguyen NQ, Fraser RJ, Bryant LK, et al: The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Crit Care Med* 2008; 36:1469–1474

429. Marik PE, Zaloga GP: Early enteral nutrition in acutely ill patients: A systematic review. *Crit Care Med* 2001; 29:2264–2270

430. Heyland DK, Dhaliwal R, Drover JW, et al: Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003; 27:355–373

431. Doig GS, Heighes PT, Simpson F, et al: Early enteral nutrition, provided within 24 hours of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: A meta-analysis of randomised controlled trials. *Intensive Care Med* 2009; 35:2018–2027

432. Taylor SJ, Fettes SB, Jewkes C, et al: Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med* 1999; 27:2525–2531

433. Ibrahim EH, Mehringer L, Prentice D, et al: Early versus late enteral feeding of mechanically ventilated patients: Results of a clinical trial. *JPEN J Parenter Enteral Nutr* 2002; 26:174–181

434. Rice TW, Mogan S, Hays MA, et al: Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med* 2011; 39:967–974

435. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Rice TW, Wheeler AP, Thompson BT, et al: Trophic vs full enteral feeding in patients with acute lung injury: The EDEN randomized trial. *JAMA* 2012; 137: 795–803

436. Arabi YM, Tamim HM, Dhar GS, et al: Permissive underfeeding and intensive insulin therapy in critically ill patients: A randomized controlled trial. *Am J Clin Nutr* 2011; 93:569–577

437. Cerra FB, McPherson JP, Konstantinides FN, et al: Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. *Surgery* 1988; 104:727–733

438. Heyland DK, MacDonald S, Keefe L, et al: Total parenteral nutrition in the critically ill patient: A meta-analysis. *JAMA* 1998; 280:2013–2019

439. Braunschweig CL, Levy P, Sheean PM, et al: Enteral compared with parenteral nutrition: A meta-analysis. *Am J Clin Nutr* 2001; 74:534–542

440. Gramlich L, Kichian K, Pinilla J, et al: Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004; 20:843–848

441. Dhaliwal R, Jurewitsch B, Harrietha D, et al: Combination enteral and parenteral nutrition in critically ill patients: Harmful or beneficial? A systematic review of the evidence. *Intensive Care Med* 2004; 30:1666–1671

442. Peter JV, Moran JL, Phillips-Hughes J: A meta-analysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Crit Care Med* 2005; 33:213–220

443. Simpson F, Doig GS: Parenteral vs. enteral nutrition in the critically ill patient: A meta-analysis of trials using the intention to treat principle. *Intensive Care Med* 2005; 31:12–23

444. Koretz RL, Avenell A, Lipman TO, et al: Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am J Gastroenterol* 2007; 102:412–429; quiz 468

445. Casaer MP, Mesotten D, Hermans G, et al: Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; 365:506–517

446. Beale RJ, Bryg DJ, Bihari DJ: Immunonutrition in the critically ill: A systematic review of clinical outcome. *Crit Care Med* 1999; 27:2799–2805

447. Heyland DK, Novak F, Drover JW, et al: Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 2001; 286:944–953

448. Montejo JC, Zarazaga A, Lopez-Martinez J, et al: Immunonutrition in the intensive care unit: A systematic review and consensus statement. *Clin Nutr* 2003; 22:221–233

449. Marik PE, Zaloga GP: Immunonutrition in critically ill patients: A systematic review and analysis of the literature. *Intensive Care Med* 2008; 34:1980–1990

450. Kieft H, Roos AN, van Drunen JD, et al: Clinical outcome of immunonutrition in a heterogeneous intensive care population. *Intensive Care Med* 2005; 31:524–532

451. Radrizzani D, Bertolini G, Facchini R, et al: Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: A randomized clinical trial. *Intensive Care Med* 2006; 32:1191–1198

452. Bertolini G, Iapichino G, Radrizzani D, et al: Early enteral immunonutrition in patients with severe sepsis: Results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med* 2003; 29:834–840

453. Suchner U, Kuhn KS, Furst P: The scientific basis of immunonutrition. *Proc Nutr Soc* 2000; 59:553-563

454. Santora R, Kozar RA: Molecular mechanisms of pharmaconutrients. *J Surg Res* 2010; 161:288–294

455. Bower RH, Cerra FB, Bershadsky B, et al: Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: Results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995; 23:436–449

456. Galban C, Montejo JC, Mesejo A, et al: An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med* 2000; 28:643–648

457. Caparros T, Lopez J, Grau T: Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet: The effect on nosocomial infections and outcome. *JPEN J Parenter Enteral Nutr* 2001; 25:299–308

458. Preiser JC, Berre PJ, Van Gossum A, et al: Metabolic effects of arginine addition to the enteral feeding of critically ill patients. *JPEN J Parenter Enteral Nutr* 2001; 25:182–187

459. Tugrul S, Ozcan PE, Akinci IO, et al: The effects of immunonutrition on the development of nosocomial infections and on clinical outcome in critically ill patients [in Turkish]. *Ulus Travma Acil Cerrahi Derg* 2004; 10:89–96

460. Novak F, Heyland DK, Avenell A, et al: Glutamine supplementation in serious illness: A systematic review of the evidence. *Crit Care Med* 2002; 30:2022–2029

461. Avenell A: Glutamine in critical care: Current evidence from systematic reviews. *Proc Nutr Soc* 2006; 65:236–241

462. Jiang H, Chen W, Hu W, et al: The impact of glutamine-enhanced enteral nutrition on clinical outcome of patients with critical illness: A systematic review of randomized controlled trials [in Chinese]. *Zhonghua Shao Shang Za Zhi* 2009; 25:325–330

463. Avenell A: Hot topics in parenteral nutrition: Current evidence and ongoing trials on the use of glutamine in critically ill patients and patients undergoing surgery. *Proc Nutr Soc* 2009; 68:261–268

464. Tian H, Wang KF, Wu TJ: Effect of total parenteral nutrition with supplementation of glutamine on the plasma diamine oxidase activity and D-lactate content in patients with multiple organ dysfunction syndrome [in Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2006; 18:616–618

465. Cai GL, Yan J, Yu YH, et al: Influence of glutamine and growth hormone intensified nutrition support on immunomodulation in critically ill elderly patients [in Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2006; 18:595–598

466. Grau T, Bonet A, Minambres E, et al: The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. *Crit Care Med* 2011; 39:1263–1268

467. Wernerman J, Kirketeig T, Andersson B, et al: Scandinavian glutamine trial: A pragmatic multi-centre randomised clinical trial of intensive care unit patients. *Acta Anaesthesiol Scand* 2011; 55:812–818

468. Fuentes-Orozco C, Anaya-Prado R, Gonzalez-Ojeda A, et al: L-alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr* 2004; 23:13–21

469. Beale RJ, Sherry T, Lei K, et al: Early enteral supplementation with key pharmaconutrients improves sequential organ failure assessment score in critically ill patients with sepsis: Outcome of a randomized, controlled, double-blind trial. *Crit Care Med* 2008; 36:131–144

470. Trial of glutamine and antioxidant supplementation in critically ill patients (REDOXS). http://clinicaltrials.gov/ct2/show/NCT00133978?term=NCT00133978&rank=1

471. Pontes-Arruda A, Demichele S, Seth A, et al: The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *JPEN J Parenter Enteral Nutr* 2008; 32:596–605

472. Pontes-Arruda A, Aragao AM, Albuquerque JD: Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* 2006; 34:2325–2333

473. Gadek JE, DeMichele SJ, Karlstad MD, et al: Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. *Crit Care Med* 1999; 27:1409–1420

474. Singer P, Theilla M, Fisher H, et al: Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med* 2006; 34:1033–1038

475. Pontes-Arruda A, Martins LF, de Lima SM, et al; Investigating Nutritional Therapy with EPA, GLA and Antioxidants Role in Sepsis Treatment (INTERSEPT) Study Group: Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in the early treatment of sepsis: Results from a multicenter, prospective, randomized, double-blinded, controlled study: The INTERSEPT study. *Crit Care* 2011; 15:R144

476. Rice TW, Wheeler AP, Thompson BT, et al: Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011; 306:1574–1581

477. Stapleton RD, Martin TR, Weiss NS, et al: A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. *Crit Care Med* 2011; 39:1655–1662

478. Grau-Carmona T, Moran-Garcia V, Garcia-de-Lorenzo A, et al: Effect of an enteral diet enriched with eicosapentaenoic acid, gamma-linolenic acid and anti-oxidants on the outcome of mechanically ventilated, critically ill, septic patients. *Clin Nutr* 2011; 30:578–584

479. Friesecke S, Lotze C, Kohler J, et al: Fish oil supplementation in the parenteral nutrition of critically ill medical patients: A randomised controlled trial. *Intensive Care Med* 2008; 34:1411–1420

480. Barbosa VM, Miles EA, Calhau C, et al: Effects of a fish oil containing lipid emulsion on plasma phospholipid fatty acids, inflammatory markers, and clinical outcomes in septic patients: a randomized, controlled clinical trial. *Crit Care* 2010; 14:R5

481. Gupta A, Govil D, Bhatnagar S, et al: Efficacy and safety of parenteral omega 3 fatty acids in ventilated patients with acute lung injury. *Indian J Crit Care Med* 2011; 15:108–113

482. Thompson BT, Cox PN, Antonelli M, et al: Challenges in end-of-life care in the ICU: Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003: Executive summary. *Crit Care Med* 2004; 32:1781–1784

483. Sprung CL, Cohen SL, Sjokvist P, et al: End of life practices in European intensive care units: The Ethicus study. *JAMA* 2003; 290:790–797

484. White DB, Engelberg RA, Wenrich MD, et al: The language of prognostication in the intensive care units. *Med Decis Making* 2010; 30:76–83

485. Nelson JE, Bassett R, Boss RD, et al, for the Improve Palliative Care in the Intensive Care Unit Project: Models for structuring a clinical initiative to enhance palliative care in the intensive care unit: A report from the IPAL-ICU Project (Improving Palliative Care in the ICU). *Crit Care Med* 2010; 38:1765–1772

486. Evans LR, Boyd EA, Malvar G, et al: Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty. *Am J Respir Crit Care Med* 2009; 179:48–53

487. Lee Char SJ, Evans LR, Malvar GL, White DB: A randomized trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. *Am J Respir Crit Care Med* 2010; 182:905–909

488. Azoulay E, Metnizt B, Sprung CL, et al: End-of-life practices in 282 intensive care units: Data from the SAPS 3 database. *Int Care Med* 2009; 35:623–630

489. Azoulay E, Timsit JF, Sprung CL, et al: Prevalence and factors of intensive care unit conflicts: The Conflicus study. *A J Resp Crit Care Med* 2009; 180:854–860

490. Bertolini G, Boffelli S, Malacarne P, et al: End-of-life decision making and quality of ICU performance: An observational study in 84 Italian units. *Int Care Med* 2010; 36:1495–1504

491. Detering KM, Hancock AD, Reade MC, Silvester W: The impact of advance care planning on end of life care in elderly patients: Randomised controlled trial. *BMJ* 2010; 340:c1345

492. Marchare Delgado E, Callahan A, Paganelli G, et al: Multidisciplinary family meetings in the ICU facilitate end-of-life decision making. *Am J Hosp Palliat Care* 2009; 26:295–302

493. Lautrette A, Darmon M, Megarbane B, et al: A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med* 2007; 356:469–478

494. Norton SA, Hogan LA, Holloway RG, et al: Proactive palliative care in the medical intensive care unit: Effect on length of stay for selected high-risk patients. *Crit Care Med* 2007; 35:1530–1535

495. Scheunemann LP, McDevitt M, Carson SS, Hanson LC: Randomized controlled trials of interventions to improve communication in intensive care: A systematic review. *Chest* 2011; 139:543–554

496. Davidson J, Powers K, Hedayat K, et al: Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force. *Crit Care Med* 2007; 35:605–622

497. Curtis JR, Treece PD, Nielsen EL, et al: Integrating palliative and critical care: Evaluation of a quality-improvement intervention. *Am J Respir Crit Care Med* 2008; 178:269–275

498. Odetola FO, Gebremariam A, Freed GL: Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. *Pediatrics* 2007; 119:487–494

499. Typpo KV, Petersen NJ, Hallman DM, et al: Day 1 multiple organ dysfunction syndrome is associated with poor functional outcome and mortality in the pediatric intensive care unit. *Pediatr Crit Care Med* 2009; 10:562–570

500. Kissoon N, Carcillo J, Espinosa V, et al; Global Sepsis Initiative Vanguard Center Contributors: World Federation of Pediatric Intensive Care and Critical Care Societies: Global sepsis initiative. *Pediatr Crit Care Med* 2011; 12:494–503

501. Goldstein B, Giroir B, Randolph A: International Pediatric Sepsis Consensus Conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8

502. Kuch BA, Carcillo JA, Han YY, Orr RA: Definitions of pediatric septic shock. *Pediatr Crit Care Med* 2005; 6:501

503. Cam BV, Tuan DT, Fonsmark L, et al: Randomized comparison of oxygen mask treatment vs nasal continuous positive airway pressure in dengue shock syndrome with acute respiratory failure. *J Trop Pediatr* 2002; 48:335–339

504. Duke T, Frank D, Mgone J: Hypoxaemia in children with severe pneumonia in Papua New Guinea. *Int J TB Lung Dis* 2000; 5:511–519

505. Pollard AJ, Britto J, Nadel S, et al: Emergency management of meningococcal disease. *Arch Dis of Child* 1999; 80:290–296

506. den Brinker M, Joosten KFM, Lime O, et al: Adrenal insufficiency in meningococcal sepsis: Bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality. *Clin Endocrinol Metab* 2005; 90:5110–5117

507. Han YY, Carcillo JA, Dragotta MA, et al: Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* 2003; 112:793–799

508. Carcillo JA, Kuch BA, Han YY, et al: Mortality and functional morbidity after use of PALS/APLS by community physicians. *Pediatrics* 2009; 124:500–508

509. Oliveira CF, Nogueira de Sá FR, Oliveira DS, et al: Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: Barriers to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support Guidelines in a pediatric intensive care unit in a developing world. *Pediatr Emerg Care* 2008; 24:810–815

510. Raimer PL, Han YY, Weber MS, et al: A normal capillary refill time of ≤ 2 seconds is associated with superior vena cava oxygen saturations of ≥ 70%. *J Pediatr* 2011; 158:968–972

511. Brierly J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666–688

512. de Oliveira CF, de Oliveira DS, Gottschald AF, et al: ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med* 2008; 34:1065–1075

513. Inwald DP, Tasker RC, Peters MJ, Nadel S: Paediatric Intensive Care Society sepsis audit. *Arch Dis Child* 2009; 94:348–353

514. Malbrain ML, De laet I, Cheatham M: Consensus conference definitions and recommendations on intra-abdominal hypertension (IAH) and the abdominal compartment syndrome (ACS): The long road to the final publications, how did we get there? *Acta Clin Belg* 2007; (Suppl):54–59

515. Cheatham ML, Malbrain ML, Kirkpatrick A, et al: Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome—Part II: Recommendations. *Intensive Care Med* 2007; 33:951–962

516. Rollins MD, Vogler SA, Mills MK, et al: Decompressive laparotomy for abdominal compartment syndrome in children: Before it is too late. *J Pediatr Surg* 2010; 45:1324–1329

517. Amado VM, Vilela GP, Queiroz A Jr, Amaral AC: Effect of a quality improvement intervention to decrease delays in antibiotic delivery in pediatric febrile neutropenia: A pilot study. *J Crit Care* 2011; 26:103.e9–103.e12

518. Cordery RJ, Roberts CH, Cooper SJ, et al: Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in the intensive care unit: antibiotic management and clinical outcome. *J Hosp Infect* 2008; 68:108–115

519. Ardura MI, Mejías A, Katz KS, et al: Daptomycin therapy for invasive Gram-positive bacterial infections in children. *Pediatr Infect Dis J* 2007; 26:1128–1132

520. Corey AL, Snyder S: Antibiotics in 30 minutes or less for febrile neutropenic patients: A quality control measure in a new hospital. *J Pediatr Oncol Nurs* 2008; 25:208–212

521. Russell NE, Pachorek RE: Clindamycin in the treatment of streptococcal and staphylococcal toxic shock syndromes. *Ann Pharmacother* 2000; 34:936–939

522. Nathwani D, Morgan M, Masterton RG, et al; British Society for Antimicrobial Chemotherapy Working Party on Community-onset MRSA Infections: Guidelines for UK practice for the diagnosis and management of methicillin-resistant Staphylococcus aureus (MRSA) infections presenting in the community. *J Antimicrob Chemother* 2008; 61:976–994

523. Gemmell CG, Edwards DI, Fraise AP, et al; Joint Working Party of the British Society for Antimicrobial Chemotherapy, Hospital Infection Society, and Infection Control Nurses Association: Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK. *J Antimicrob Chemother* 2006; 57:589–608

524. Cawley MJ, Briggs M, Haith LR Jr, et al: Intravenous immunoglobulin as adjunctive treatment for streptococcal toxic shock syndrome associated with necrotizing fasciitis: case report and review. *Pharmacotherapy* 1999; 19:1094–1098

525. Rodríguez-Nuñez A, Dosil-Gallardo S, Jordan I; Ad Hoc Streptococcal Toxic Shock Syndrome Collaborative Group of the Spanish Society of Pediatric Intensive Care: Clinical characteristics of children with group A streptococcal toxic shock syndrome admitted to pediatric intensive care units. *Eur J Pediatr* 2011; 170:639–644.

526. Paganini HR, Della Latta P, Soto A, et al: Community-acquired Staphylococcus aureus bacteremia: 17 years of experience in Argentine children [in Spanish]. *Arch Argent Pediatr* 2010; 108:311–317

527. Tilanus AM, de Geus HR, Rijnders BJ, et al: Severe group A streptococcal toxic shock syndrome presenting as primary peritonitis: A case report and brief review of the literature. *Int J Infect Dis* 2010; 14(Suppl 3):e208–e212

528. Newland JG, Kearns GL: Treatment strategies for methicillin-resistant Staphylococcus aureus infections in pediatrics. *Paediatr Drugs* 2008; 10:367–378

529. Barie PS, Williams MD, McCollam JS, et al: Benefit/risk profile of drotrecogin alfa (activated) in surgical patients with severe sepsis. *Am J Surg* 2004; 188:212–220

530. Barie PS, Hydo LJ, Shou J, Eachempati SR: Efficacy and safety of drotrecogin alfa (activated) for the therapy of surgical patients with severe sepsis. *Surg Infect* 2006; 7(Suppl 2):S77–S80

531. Marshall JC, Maier RV, Jimenez M, Dellinger EP: Source control in the management of severe sepsis and septic shock: An evidence-based review. *Crit Care Med* 2004; 32(Suppl 11):S513–S526

532. Penington AJ, Craft RO, Tilkorn DJ: Plastic surgery management of soft tissue loss in meningococcal septicemia: Experience of the Melbourne Royal Children's Hospital. *Ann Plast Surg* 2007; 58:308–314

533. Wheeler JS, Anderson BJ, De Chalain TM: Surgical interventions in children with meningococcal purpura fulminans: A review of 117 procedures in 21 children. *J Pediatr Surg* 2003; 38:597–603

534. Jackson MA, Colombo J, Boldrey A: Streptococcal fasciitis with toxic shock syndrome in the pediatric patient. *Orthop Nurs* 2003; 22:4–8

535. Xiao-Wu W, Herndon DN, Spies M, et al: Effects of delayed wound excision and grafting in severely burned children. *Arch Surg* 2002; 137:1049–1054

536. Haecker FM, Berger D, Schumacher U, et al: Peritonitis in childhood: Aspects of pathogenesis and therapy. *Pediatr Surg Int* 2000; 16:182–188

537. Gwynne-Jones DP, Stott NS: Community-acquired methicillin-resistant Staphylococcus aureus: A cause of musculoskeletal sepsis in children. *J Pediatr Orthop* 1999; 19:413–416

538. Wu MH, Tseng YL, Lin MY, Lai WW: Surgical treatment of pediatric lung abscess. *Pediatr Surg Int* 1997; 12:293–295

539. Murphy JJ, Granger R, Blair GK, et al: Necrotizing fasciitis in childhood. *J Pediatr Surg* 1995; 30:1131–1134

540. Jaber MR, Olafsson S, Fung WL, Reeves ME: Clinical review of the management of fulminant clostridium difficile infection. *Am J Gastroenterol* 2008; 103:3195–3203

541. Ananthakrishnan AN: Clostridium difficile infection: Epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol* 2011; 8:17–26

542. Olivas AD, Umanskiy K, Zuckerbraun B, Alverdy JC: Avoiding colectomy during surgical management of fulminant Clostridium difficile colitis. *Surg Infect* 2010; 11:299–305

543. Ngo NT, Cao XT, Kneen R, et al: Acute management of dengue shock syndrome: A randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001; 32:204–213

544. Willis BA, Dung NM, Loan HT, et al: Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; 353:877–889

545. Dung NM, Day NP, Tam DT, et al: Fluid replacement in dengue shock syndrome: A randomized, double-blind comparison of four intravenous-fluid regimens. *Clin Infect Dis* 1999; 29:787–794

546. Booy R, Habibi P, Nadel S, et al: Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001; 85:386–390

547. Maat M, Buysse CM, Emonts M, et al. Improved survival of children with sepsis and purpura: Effects of age, gender and era. *Crit Care* 2007; 11:R112

548. Cruz AT, Perry AM, Williams EA, et al: Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics* 2011; 127:e758–e766

549. Maitland K, Kiguli S, Opoka RO, et al: FEAST trial group mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 354:2483–2495

550. Kanter RK, Zimmerman JJ, Strauss RH, et al: Pediatric emergency intravenous access: Evaluation of a protocol. *Am J Dis Child* 1986; 140:132–134

551. Carcillo JA, Davis AL, Zaritsky A: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; 266:1242–1245

552. Ranjit S, Kissoon N, Jayakumar I: Aggressive management of dengue shock syndrome may decrease mortality rate: A suggested protocol. *Pediatr Crit Care Med* 2005; 6:412–419

553. Akech S, Ledermann N, Maitland K: Choice of fluids for resuscitation in children with severe infection and shock; Systematic review. *BMJ* 2010; 341:c4416

554. Santhanam I, Sangareddi S, Venkataraman S, et al: A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. *Pediatr Emerg Care* 2008; 24:647–655

555. Ninis N, Phillips C, Bailey L, et al: The role of healthcare delivery in the outcome of meningococcal disease in children: Case-control study of fatal and non-fatal meningococcal disease in children. *BMJ* 2005; 330:1475

556. Thompson MJ, Ninis N, Perera R, et al: Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; 367:397–403

557. Ceneviva G, Paschall JA, Maffei F, et al: Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics* 1998; 102:e19

558. Choong K, Bohn D, Fraser DD, et al; Canadian Critical Care Trials Group: Vasopressin in pediatric vasodilatory shock: A multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2009; 180:632–639

559. Yildizdas D, Yapicioglu H, Celik U, et al: Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children. *Intensive Care Med* 2008; 34:511–517

560. Rodriguez-Nunez A, Lopez-Herce J, Gil-Anton J, et al; RETSPED Working Group of the Spanish Society of Pediatric Intensive Care: Rescue treatment with terlipressin in children with refractory septic shock: A clinical study. *Crit Care* 2006; 10:R20

561. Rodríguez-Núñez A, Oulego-Erroz I, Gil-Antón J, et al: Continuous terlipressin infusion as rescue treatment in a case series of children with refractory septic shock. *Ann Pharmacother* 2010; 44:1545–1553

562. Keeley SR, Bohn DJ: The use of inotropic and afterload-reducing agents in neonates. *Clin Perinatol* 1988; 15:467–489

563. Barton P, Garcia J, Kouatli A, et al: Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock: A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996; 109:1302–1312

564. Lindsay CA, Barton P, Lawless S, et al: Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; 132:329–334

565. Irazuzta JE, Pretzlaff RK, Rowin ME: Amrinone in pediatric refractory septic shock: An open-label pharmacodynamic study. *Pediatr Crit Care Med* 2001; 2:24–28

566. Powell KR, Sugarman LI, Eskenazi AE, et al: Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr* 1991; 117:515–522

567. Ringe HI, Varnholt V, Gaedicke G: Cardiac rescue with enoximone in volume and catecholamine refractory septic shock. *Pediatr Crit Care Med* 2003; 4:471–475

568. Morelli A, Donati A, Ertmer C, et al: Levosimendan for resuscitating the microcirculation in patients with septic shock: A randomized controlled study. *Crit Care* 2010; 14:R232

569. Namachivayam P, Crossland DS, Butt WW, Shekerdemian LS: Early experience with Levosimendan in children with ventricular dysfunction. *Pediatr Crit Care Med* 2006; 7:445–448. Erratum in: *Pediatr Crit Care Med* 2007; 8:197

570. Magliola R, Moreno G, Vassallo JC, et al: Levosimendan, a new inotropic drug: Experience in children with acute heart failure [in Spanish]. *Arch Argent Pediatr* 2009; 107:139–145

571. Harris E, Schulzke SM, Patole SK: Pentoxifylline in preterm neonates: A systematic review. *Paediatr Drugs* 2010; 12:301–311

572. Meyer DM, Jessen ME: Results of extracorporeal membrane oxygenation in children with sepsis: The Extracorporeal Life Support Organization. *Ann Thorac Surg* 1997; 63:756–761

573. Goldman AP, Kerr SJ, Butt W, et al: Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. *Lancet* 1997; 349:466–469

574. Maclaren G, Butt W, Best D, Donath S: Central extracorporeal membrane oxygenation for refractory pediatric septic shock. *Pediatr Crit Care Med* 2011; 12:133–136

575. Oda T, Yasunaga H, Tsutsumi Y, et al: A child with influenza A (H1N1)-associated myocarditis rescued by extracorporeal membrane oxygenation. *J Artif Organs* 2010; 13:232–234

576. Norfolk SG, Hollingsworth CL, Wolfe CR, et al: Rescue therapy in adult and pediatric patients with pH1N1 influenza infection: A tertiary center intensive care unit experience from April to October 2009. *Crit Care Med* 2010; 38:2103–2107

577. Flagg A, Danziger-Isakov L, Foster C, et al: Novel 2009 H1N1 influenza virus infection requiring extracorporeal membrane oxygenation in a pediatric heart transplant recipient. *J Heart Lung Transplant* 2010; 29:582–584

578. Kumar A, Zarychanski R, Pinto R, et al; Canadian Critical Care Trials Group H1N1 Collaborative: Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009; 302:1872–1879

579. Pizarro CF, Troster EJ, Damiani D, et al: Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 2005; 33:855–859

580. Riordan FA, Thomson AP, Ratcliffe JM, et al: Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: Evidence of adrenal insufficiency? *Crit Care Med* 1999; 27:2257–2261

581. De Kleijn ED, Joosten KF, Van Rijn B, et al: Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations is associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J* 2002; 21:330–336

582. Markovitz BP, Goodman DM, Watson S, et al: A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: What is the role of steroids? *Pediatr Crit Care Med* 2005; 6:270–274

583. Pizarro CF, Troster EJ: Adrenal function in sepsis and septic shock. *J Pediatr* (Rio J) 2007; 83(Suppl 5):S155–S162

584. Zimmerman JJ, Williams MD: Adjunctive corticosteroid therapy in pediatric severe sepsis: Observations from the RESOLVE study. *Pediatr Crit Care Med* 2011; 12:2–8

585. Lacroix J, Hebert PC, Hutchison JS, et al: Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007; 256:1609–1619

586. Karam O, Tucci M, Ducruet T, et al, for the Canadian Critical Care Trials Group and the PALISI Network: Red blood cell transfusion thresholds in pediatric patients with sepsis. *Pediatr Crit Care Med* 2011; 12:512–518

587. Church GD, Matthay MA, Liu K, et al: Blood product transfusions and clinical outcomes in pediatric patients with acute lung injury. *Pediatr Crit Care Med* 2009; 10:297–302

588. López-Herce Cid J, Bustinza Arriortúa A, Alcaraz Romero A, et al: Treatment of septic shock with continuous plasma filtration and hemodiafiltration [in Spanish]. *An Pediatr* 2003; 59:491–496

589. Stegmayr BG, Banga R, Berggren L, et al: Plasma exchange as rescue therapy in multiple organ failure including acute renal failure. *Crit Care Med* 2003; 31:1730–1736

590. El-Nawawy A, Abbassy AA, El-Bordiny M, Essawi S: Evaluation of early detection and management of disseminated intravascular coagulation among Alexandria University pediatric intensive care patients. *J Trop Pediatr* 2004; 50:339–347

591. Campanelli A, Kaya G, Ozsahin AH, et al: Purpura fulminans in a child as a complication of chicken pox infection. *Dermatology* 2004; 208:262–264

592. Muntean W: Fresh frozen plasma in the pediatric age group and in congenital coagulation factor deficiency. *Thromb Res* 2002; 107(Suppl 1):S29–S32. Review

593. Sánchez Miralles A, Reig Sáenz R, Marco Vera P, et al: Abnormalities in coagulation and fibrinolysis in septic shock with purpura [in Spanish]. *An Esp Pediatr* 2002; 56:99–10

594. Hazelzet JA, Risseeuw-Appel IM, Kornelisse RF, et al: Age-related differences in outcome and severity of DIC in children with septic shock and purpura. *Thromb Haemost* 1996; 76:932–938

595. Churchwell KB, McManus ML, Kent P, et al: Intensive blood and plasma exchange for treatment of coagulopathy in meningococcemia. *J Clin Apher* 1995; 10:171–177

596. Ala FA, Greaves M, Jones J, et al: Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. *Curr Vasc Pharmacol* 2009; 7:110–119

597. Meyer B, Hellstern P: Recommendations for the use of therapeutic plasma. *Semin Nephrol* 2008; 28:447–456

598. Fortenberry JD: Pediatric critical care management of septic shock prior to acute kidney injury and renal replacement therapy. *Semin Nephrol* 2008; 28:447–456

599. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, et al; British Committee for Standards in Haematology, Blood Transfusion Task Force. Practical guidelines for the clinical use of plasma. *Thromb Res* 2002; 107(Suppl 1):S53–S57

600. Muntean W, Schramm W, Seifried E, Solheim BG: Guideline for the use of fresh-frozen plasma. Medical Directors Advisory Committee, National Blood Transfusion Council. *S Afr Med J* 1998; 88:1344–1347

601. Nguyen TC, Han YY: Plasma exchange therapy for thrombotic microangiopathies. *Organogenesis* 2011; 1:28–31

602. van Deuren M, Brandtzaeg P, van der Meer JW: Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev* 2000; 13:144–166

603. Scharfman WB, Tillotson JR, Taft EG, Wright E: Plasmapheresis for meningococcemia with disseminated intravascular coagulation. *N Engl J Med* 1979; 300:1277–1278

604. van Deuren M, Santman FW, van Dalen R, et al: Plasma and whole blood exchange in meningococcal sepsis. *Clin Infect Dis* 1992; 15:424–430

605. Bjorvatn B, Bjertnaes L, Fadnes HO, et al: Meningococcal septicaemia treated with combined plasmapheresis and leucapheresis or with blood exchange. *Br Med J* 1984; 288:439–441

606. Brandtzaeg P, Sirnes K, Folsland B, et al: Plasmapheresis in the treatment of severe meningococcal or pneumococcal septicaemia with DIC and fibrinolysis: Preliminary data on eight patients. *Scand J Clin Lab Invest* 1985; 178(Suppl):53–55

607. Drapkin MS, Wisch JS, Gelfand JA, et al: Plasmapheresis for fulminant meningococcemia. *Pediatr Infect Dis J* 1989; 8:399–400

608. Schott U, Bjorsell-Ostling E: Sonoclot coagulation analysis and plasma exchange in a case of meningococcal septicaemia. *Can J Anaesth* 1995; 42:64–68

609. Mok Q, Butt W: The outcome of children admitted to intensive care with meningococcal septicaemia. *Intensive Care Med* 1996; 22:259–263

610. Kumar A, Kanagasundaram NS, Collyns TA, Davison AM: Plasma exchange and haemodiafiltration in fulminant meningococcal sepsis. *Nephrol Dial Transplant* 1998; 13:484–487

611. Muntean C, Bloodworth LL, Korn TH: Antithrombin concentrate with plasma exchange in purpura fulminans. *Pediatr Crit Care Med* 2000; 1:84–87

612. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: A prospective, randomised, controlled trial. *Intensive Care Med* 2002; 28:1434–1439

613. Randolph AG: Management of acute lung injury and acute respiratory distress syndrome in children. *Crit Care Med* 2009; 37:2448–2454

614. Krishnan J, Morrison W: Airway pressure release ventilation: A pediatric case series. *Pediatr Pulmonol* 2007; 42:83–88

615. Ten IS, Anderson MR: Is high-frequency ventilation more beneficial than low-tidal volume conventional ventilation? *Respir Care Clin N Am* 2006; 12:437–451

616. Rotta AT, Steinhorn DM: Is permissive hypercapnia a beneficial strategy for pediatric acute lung injury? *Respir Care Clin N Am* 2006; 12:371–387

617. Ben Jaballah N, Khaldi A, Mnif K, et al: High-frequency oscillatory ventilation in pediatric patients with acute respiratory failure. *Pediatr Crit Care Med* 2006; 7:362–367

618. Cam PC, Cardone D: Propofol infusion syndrome. *Anaesthesia* 2007; 62:690–701

619. Parke TJ, Stevens JE, Rice AS, et al: Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. *BMJ* 1992; 305:613–616

620. den Brinker M, Hokken-Koelega AC, Hazelzet JA, et al: One single dose of etomidate negatively influences adrenocortical performance for at least 24h in children with meningococcal sepsis. *Intensive Care Med* 2008; 34:163–168

621. Su F, Hammer GB: Dexmedetomidine: Pediatric pharmacology, clinical uses and safety. *Expert Opin Drug Saf* 2011; 10:55–66

622. Carcillo JA, Doughty L, Kofos D, et al: Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. *Intensive Care Med* 2003; 29:980–984

623. Branco RG, Garcia PC, Piva JP, et al: Glucose level and risk of mortality in pediatric septic shock. *Pediatr Crit Care Med* 2005; 6:470–472

624. Faustino EV, Apkon M: Persistent hyperglycemia in critically ill children. *J Pediatr* 2005; 146:30–34

625. Jeschke MG, Kulp GA, Kraft R, et al: Intensive insulin therapy in severely burned pediatric patients: A prospective randomized trial. *Am J Respir Crit Care Med* 2010; 182:351–359

626. Day KM, Haub N, Betts H, Inwald DP: Hyperglycemia is associated with morbidity in critically ill children with meningococcal sepsis. *Pediatr Crit Care Med* 2008; 9:636–640

627. Garcia Branco R, Tasker RC, Ramos Garcia PC, et al: Glycemic control and insulin therapy in sepsis and critical illness. *J Pediatr* (Rio J) 2007; 83(Suppl 5):S128–S136

628. Verhoeven JJ, den Brinker M, Hokken-Koelega AC, et al: Pathophysiological aspects of hyperglycemia in children with meningococcal sepsis and septic shock: A prospective, observational cohort study. *Crit Care* 2011; 15:R44

629. Vlasselaers D, Milants I, Desmet L, et al: Intensive insulin therapy for patients in paediatric intensive care: A prospective, randomised controlled study. *Lancet* 2009; 373:547–556

630. Foland JA, Fortenberry JD, Warshaw BL, et al: Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. *Crit Care Med* 2004; 32:1771–1776

631. Santiago MJ, López-Herce J, Urbano J, et al: Clinical course and mortality risk factors in critically ill children requiring continuous renal replacement therapy. *Intensive Care Med* 2010; 36:843–849

632. Brophy PD: Renal supportive therapy for pediatric acute kidney injury in the setting of multiorgan dysfunction syndrome/sepsis. *Semin Nephrol* 2008; 28:457–469

633. Krafte-Jacobs B, Sivit CJ, Mejia R, et al: Catheter-related thrombosis in critically ill children: Comparison of catheters with and without heparin bonding. *J Pediatr* 1995; 126:50–54

634. Pierce CM, Wade A, Mok Q: Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Med* 2000; 26:967–972

635. Chaïbou M, Tucci M, Dugas MA, et al: Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: A prospective study. *Pediatrics* 1998; 102:933–938

636. Gauvin F, Dugas M, Chaïbou M, et al: The impact of clinically significant upper gastrointestinal bleeding in a pediatric intensive care unit. *Pediatr Crit Care Med* 2001; 2:294–298

637. Sheridan RL, Yu YM, Prelack K, et al: Maximal parenteral glucose oxidation in hypermetabolic young children: A stable isotope study. *JPEN J Parenter Enteral Nutr* 1998; 22:212–216

APPENDIX A

2012 SSC Guidelines Committee

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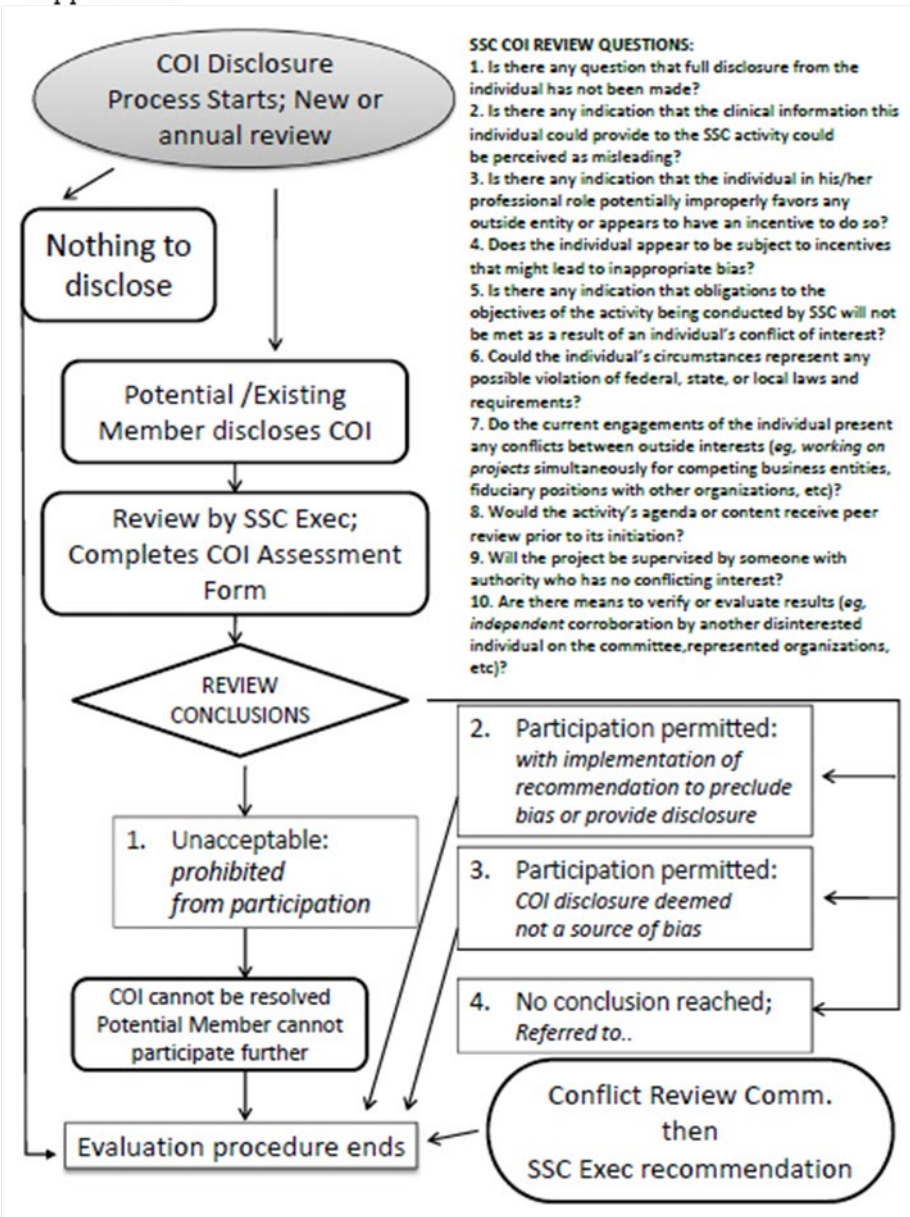
Pediatric Subgroup

Jan Hazelzet, Adrienne Randolph, Margaret Parker, Ann Thompson, Paolo Biban, Alan Duncan, Cris Mangia, Niranjan Kissoon, and Joseph Carcillo

Appendix B


COI Disclosure Process Starts; New or annual review
Nothing to disclose
Potential /Existing Member discloses COI
Review by SSC Exec; Completes COI Assessment Form
REVIEW CONCLUSIONS
1. Unacceptable: prohibited from participation
COI cannot be resolved Potential Member cannot participate further
Evaluation procedure ends
2. Participation permitted: with implementation of recommendation to preclude bias or provide disclosure
3. Participation permitted: COI disclosure deemed not a source of bias
4. No conclusion reached; Referred to..
Conflict Review Comm. then SSC Exec recommendation
SSC COI REVIEW QUESTIONS:
1. Is there any question that full disclosure from the individual has not been made?
2. Is there any indication that the clinical information this individual could provide to the SSC activity could be perceived as misleading?
3. Is there any indication that the individual in his/her professional role potentially improperly favors any outside entity or appears to have an incentive to do so?
4. Does the individual appear to be subject to incentives that might lead to inappropriate bias?
5. Is there any indication that obligations to the objectives of the activity being conducted by SSC will not be met as a result of an individual's conflict of interest?
6. Could the individual's circumstances represent any possible violation of federal, state, or local laws and requirements?
7. Do the current engagements of the individual present any conflicts between outside interests (eg, working on projects simultaneously for competing business entities, fiduciary positions with other organizations, etc)?
8. Would the activity's agenda or content receive peer review prior to its initiation?
9. Will the project be supervised by someone with authority who has no conflicting interest?
10. Are there means to verify or evaluate results (eg, independent corroboration by another disinterested individual on the committee,represented organizations, etc)?

Appendix C. ARDSnet Ventilator Management

~~Appendix C. ARDSnet Ventilator Management~~

- Assist control mode—volume ventilation
- Reduce tidal volume to 6 mL/kg lean body weight
- Keep Pplat <30 cm H_2O
  —Reduce TV as low as 4 mL/kg predicted body weight to limit Pplat
- Maintain SaO_2/SpO_2 88%–95%
- Anticipated PEEP settings at various FIO_2 requirements

FiO2	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]

TV, tidal volume; SaO_2, arterial oxygen saturation; PEEP, positive end-expiratory pressure.

1- The 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 of water
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	
PaO2	55- 80 mm Hg
SpO2	88 - 95%
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP < 8 cm of water and FiO2 < 0.40

Allowable combinations of PEEP and FiO2†

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

FiO2	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

* Complete ventilator procedures and eligibility criteria are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org) and at www.ardsnet.org. PaO2 denotes partial pressure of arterial oxygen, SpO2 oxyhemoglobin saturation as measured by pulse oximetry, FiO2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

† In both study groups (lower and higher PEEP), additional increases in PEEP to 34 cm of water were allowed but not required after the FiO2 had been increased to 1.0 according to the protocol.

Adapted from: Brower RG, Lanken PN, MacIntyre N, Matthay MA, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome.N Engl J Med. 2004 Jul 22;351(4):327-36.

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 >2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12,000 μL^{-1})
Leukopenia (WBC count <4000 μL^{-1})
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FIO_2 <300)
Acute oliguria (urine output <0.5 mL/kg hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase >0.5 mg/dL or 44.2 micromol/L
Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure INR, international normalized ration; a PTT, 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

Table 2

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 >upper limits lab normal
- Urine output <0.5 ml/kg hr for >2 hr despite adequate fluid resuscitation
- ALI with PaO2/FIO2 <250 in the absence of pneumonia as infection source
- ALI with PaO2/FIO2 <200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dl (176.8 micromol/L)
- Bilirubin >2 mg/dl (34.2 micromol/L)
- Platelet count <100,000
- Coagulopathy (INR >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

Table 3. Determination of the quality of evidence

- **Underlying methodology**

A (high)	RCT
B (moderate)	Downgraded RCT or upgraded observational studies
C (low)	Well-done observationalstudies with controls
D (very low)	Case series or expert opinion

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

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

*****RCT= randomized controlled trial; RR=relative risk

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 is a strong recommendation.
Certainty about the balance of benefits versus 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 is 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 that is considered and other costs related to the decision – that is, fewer resources consumed – the more likely is a strong recommendation.

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 $mL \cdot kg^{-1} \cdot hr^{-1}$
(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 as rapidly as possible (grade 2C).

B. Screening for Sepsis and Performance Improvement
1. Routine screening of 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 minutes) 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 hr.) 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 (grade1C).

D. Antimicrobial Therapy
1. Intravenous antimicrobial therapy started as early as possible and within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C).

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 de-escalation (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).

4b. Empiric combination therapy should not be administered for >3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 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 not be used in patients with severe inflammatory states determined to be of noninfectious cause (grade 1C).

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 intevention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. When infected peri-pancreatic 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 (SOD) and selective digestive decontamination (SDD) 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 (CHG) be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

Table 6: Norepinephrine Compared to Dopamine in Severe Sepsis Summary of Evidence Table

Norepinephrine compared to 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. NEJM 2010;362:779-89; Marik PE. JAMA 1994;272:1354-7; Mathur RDAC. Indian Journal of Critical Care Medicine 2007;11:186-91; Martin C. Chest 1993;103:1826-31; Patel GP. Shock 2010;33:375-80; Ruokonen E. Crit Care Med1993;21:1296-303.

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Dopamine	Corresponding risk Norepinephrine	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Short-term mortality	**Study population**		**RR 0.91** (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	530 per 1000	**482 per 1000** (440 to 524)				
Serious adverse events - Supraventricular arrhythmias	**Study population**		**RR 0.47** (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	229 per 1000	**82 per 1000** (34 to 195)				
Serious adverse events - Ventricular arrhythmias	**Study population**		**RR 0.35** (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	39 per 1000	**15 per 1000** (8 to 27)				

*The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) 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

[1] Strong heterogeneity in the results (I squared = 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.
[2] Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, NEJM 2010. We have lowered the quality of evidence one level for indirectness.

coronary artery due to ARDS Table 7. Recommendations: Hemodynamic Support and Adjunctive

Support

G. Fluid Therapy of Severe Sepsis
1. We recommend crystalloids be used in the initial fluid resuscitation of severe sepsis and septic shock. (grade 1A).

2. We suggest adding albumin in the initial fluid resuscitation **of** severe sepsis and septic shock in patients who require repeated boluses of crystalloids (grade 2B).

3. We recommend against the use of hydroxyethyl ethyl starches (grade 1B).

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).

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

2. Norepinephrine as the first choice vasopressor (grade 1B).

3. Epinephrine when an additional agent is needed to maintain adequate blood pressure and to wean off norepinephrine as MAP allows (grade1C).

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 arrhythmias and low heart rate). (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 mean arterial pressure (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. We suggest treated patients have the hydrocortisone tapered when vasopressors are no longer required (grade 2D).

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

5. When hydrocortisone is given to treat septic shock, we suggest using continuous infusion rather than repetitive bolus injections (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 $\leq$10,000/mm^3 (10 x 10^9/L) in the absence of apparent bleeding. We suggest prophylactic platelet transfusion when counts are $\leq$ 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 rather than 12 ml/kg predicted body weight in patients with sepsis-induced ARDS (grade 1A).

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 severe sepsis induced 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 PaO2/FiO2 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 ALI/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 acute lung injury 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 ALI/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. A short course of NMBA of not greater than 48 hours for patients *with* early, severe sepsis-induced ARDS (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. We recommend that blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (grade 1C).

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).

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). We recommend that this be accomplished with daily subcutaneous low-molecular

weight heparin (LMWH) (1B versus twice daily UFH and 2C versus three times daily UFH). If creatinine clearance is <30 ml/min and LMWH is used, 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. 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 1A).

2. When stress ulcer prophylaxis is used, we suggest the use of proton pump inhibitors rather than H2RA (grade 2C)

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 cal 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).

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 be capillary refill of $\leq$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. Superior vena cava O_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 Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock (grade 1C).
The ACCM-PALS guidelines are summarized in Figure 2. (502-504)

4. Evaluate for and reverse pneumothorax, pericardial tamponade, intra-abdominal hypertension, 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) and Inhaled Nitric Oxide
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 1 A) .

G. Protein C and Activated Protein Concentrate
No recommendation as no longer available

I. 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).

J. Mechanical Ventilation
1. Llung-protective strategies during mechanical ventilation (grade 2C).

K Sedation/Analgesia/DrugToxicities
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).

L. 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).

M Diuretics and Renal Replacement Therapy
1. Use diuretics to reverse fluid overload, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent > 10% total body weight fluid overload (grade 2C).

O. Deep Vein Thrombosis (DVT) Prophylaxis
No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

P. Stress Ulcer(SU) Prophylaxis
No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis

Q. Nutrition
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

Figure 1 – Mortality in clinical trials of intensive insulin therapy by high or moderate control groups

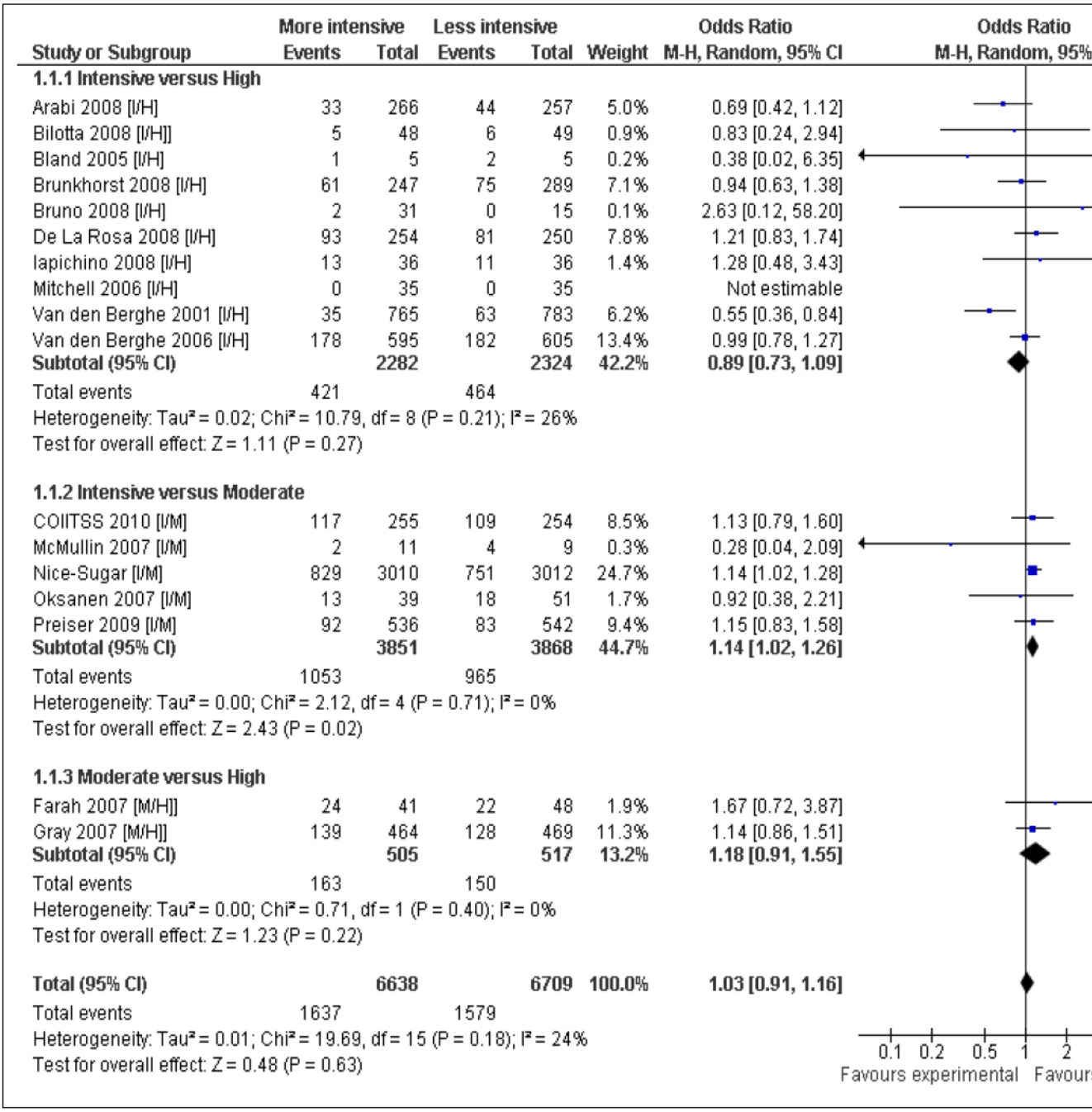
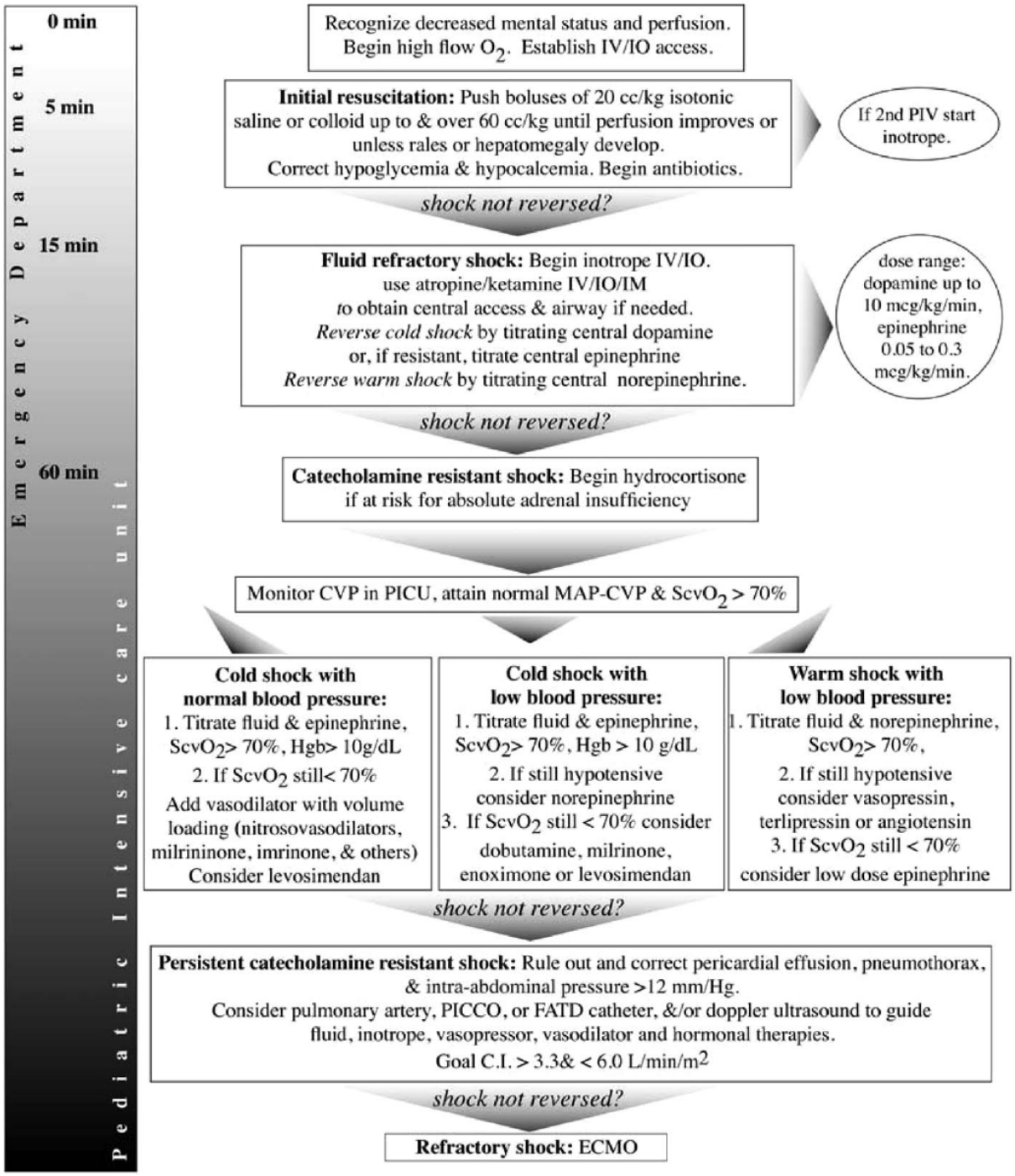


Figure 2. Algorithm for time sensitive, goal-directed stepwise management of hemodynamic



support in infants and children.

Figure 1. Surviving Sepsis Campaign Care Bundles.

WITHIN 3 HOURS OF SEVERE SEPSIS:

1) Measure lactate level

2) Obtain blood cultures prior to adminiatration of antibiotics

3) Administer broad spectrum antibiotics

4) Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

WITHIN 6 HOURS OF INITIAL SYMPTOMS FOR SEPTIC SHOCK:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP)≥65mmHg)

6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36mg/dl):

- Achievecentral venous pressure (CVP) of ≥8 mm Hg

- Achieve central venous oxygen saturation (ScvO2) of ≥70%

7) Remeasure lactate if initial lactate was elevated

Online Appendix A

SSC Conflict of Interest Policy:

The SSC Guidelines Committee developed and adopted a comprehensive conflict of interest (COI) policy at the commencement of the current update process. This policy was established to ensure that SSC managed real and potential COI (both financial land non-financial) in an open and effective manner in order to secure and preserve transparency and public trust in the integrity of SSC processes and products. The comprehensive policies and standards for the management of COI applied to all subcommittees, work groups, task forces, evidence process panels, and writing panels as well as individual volunteers, liaisons, staff, and others involved in SSC Guidelines Committee work.

The goals of the COI policy were (a) to enhance the objectivity, scientific rigor and transparency of official SSC statements, guidelines and documents by providing an explicit methodology for individuals and participating organizations to identify and disclose all personal or institutional "competing interests" that may cause or be perceived as causing a COI affecting the individual's participation in the activity, and resolve all conflicts of interest and (b) to provide for disclosure and resolution of conflicts of interest in a manner respectful of the SSC participating organizations and other individuals essential to SSC activities, and respectful of confidentiality to the extent appropriate.

Individual participants were required to provide a written disclosure of all potential conflicts of interest (both financial and non-financial) by completing the International Committee of Medical Journal Editors (ICMJE) Uniform Disclosure Form for Potential Conflicts of Interest. While committee members were encouraged to specify remuneration of any dollar amounts, this was not mandatary. A separate questionnaire was developed to record non-financial COI including an

assessment of each participants approach to the use of guidelines and incorporation of evidence into clinical decision making in sepsis.

Updates were required whenever material changes occurred in the individual's status. Processes were established for review and adjudication of COI (Appendix B of primary document). Individuals with COI in a particular area or topic who were selected for a leadership role with oversight or responsibility for that area or topic were subject to heightened adjudication by the executive committee. The executive reviewed initial disclosures before deciding on participants, and excluded participants if there was a non-resolvable conflict of interest. The chair of each subgroup and more than 50% of the members of each group were required to be free of any relevant relationship with industry and of any significant nonfinancial COI or competing organizational relationship. Any chair of a writing group with any relevant COI was asked to step down as a chair.

During in-person meetings and telephone conference calls, each individual was required to make a verbal statement each time they spoke regarding their potential COI. Any individuals with a financial conflict relative to the subject matter about to be discussed were asked to recuse themselves from the deliberation, unless they had special information of a technical nature. Formal abstention from all votes and actions was required for any individual with a potential recorded COI.

Authors' Disclosure Information:

Dr. Aitken disclosed that she has no potential conflicts of interest. Her non-financial disclosures include publications on protocol directed sedation and nursing considerations to complement the Surviving Sepsis Campaign guidelines.

Dr. Al Rahma disclosed that he has no potential conflicts of interest.
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) and received a consulting income (anti-TRL4 therapy for severe sepsis) from Eisai, Inc. Travel/accommodation expenses were reimbursed by Eisai, Inc. Additionally, he is the primary investigator for an ongoing National Institutes of Health-funded study comparing early resuscitation strategies for sepsis induced tissue hypoperfusion.

Dr. Annane participated on the Fresenius Kabi International Advisory Board (honorarium 2000€). His non-financial 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 versus norepinephrine (CATS study) – *Lancet* 2007. He also is the principle investigator of an ongoing investigator-led multinational randomized controlled trial of crystalloids versus colloids (Crystal Study).

Dr. Beale received compensation for his participation as board member for Eisai, Inc, Applied Physiology, bioMérieux, Covidien, SIRS-Lab, and Novartis. Consulting income 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). He received honoraria (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 non-financial disclosures include authorship of the position statement on fluid resuscitation from the ESICM task force on colloids (yet to be finalized).

Dr. Bernard received compensation for his participation as a board member of Cumberland Pharmaceuticals, Nashville, TN ($50,000-$100,000- no known conflict with any topic area); and AstraZeneca ($1,000-$5,000 - paid consultancy ended in 2009). He received grant support from AstraZeneca ($100,000 - grant is in support of the study on statins in the treatment of H1N1 influenza). He has stock/stock options in Cumberland Pharmaceuticals (no known conflict with topic area). Vanderbilt University was the coordinating center for the PROWESS Shock trial (Eli Lilly-income support commensurate with 1% to 5% effort on the project. His non-financial disclosures include initial authorship of the PROWESS trial of aPC in sepsis.

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

Dr. Bion received grant support for being the senior clinical leader of the National Patient Safety Agency's 'Matching Michigan' project.

Dr. Calandra reports grant support from Baxter (research grant on testing of anti-MIF monoclonal antibodies for treatment of sepsis); bioMérieux (development of diagnostic tests for fungal infections—money to research foundation); Merck Sharp & Dohme-Chibret AG (grant for medical mycology); and Roche Diagnostics (research grant for SeptiFast). He consulted for Astellas (speaker and chairperson at company sponsored symposium [ESICM 2009 and ISICEM 2010- antifungal therapy]); Baxter (anti-MIF monoclonal antibodies for treatment of sepsis); bioMérieux (diagnostic tests for infectious diseases); Essex Chemie AG (advisory board); Evolva (advisory board); Merck Sharp & Dohme-Chibret AG (antifungal agents, and was on the advisory board of a chairperson meeting); and Pfizer (speaker at meeting). He also reports monetary compensation for his participation in review activities (data monitoring boards, statistical analysis, end point committees [Eisai - steering committee; Eritoran Clinical Trial; PPD; Novartis]). His institution received grant support from the Swiss National Science Foundation. Furthermore, he is a member of the Research Council of the Swiss National Science Foundation. His non-financial disclosures include authorship of review articles on the use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis.

Dr. Carcillo received grant support from the National Institutes of Health and holds a patent from the University of Pittsburgh. His non-financial disclosures include authorship of the ACCM-PALS guideline and publications on the management of sepsis and shock in children.

Dr. Clemmer has non-financial conflicts as a member of ARDSNet since its inception and is a contributor to many of its publications. He developed a protocol for the standard use of APRV for local use. Additionally, he has published and lectured on the removal of sedation and early ambulation of mechanically ventilated patients.

Dr. Dellinger consulted for Biotest (immunoglobin concentrate available in Europe for potential use in sepsis); and AstraZeneca (anti-TNF compound in sepsis clinical trial). His institution received consulting income from IKARIA (inhaled nitric oxide available for off label use in

ARDS) and grant support from Spectral Diagnostics Inc. (endotoxin removal clinical trial); Ferring (vasopressin analog clinical trial-ongoing); and AstraZeneca (anti-TNF clinical trial-ongoing). He received payment for educational presentations, including service on the speakers bureau from Eisai (anti-endotoxin compound in clinical trial).

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

Dr. Divatia received unrestricted education grants to his institution (Edwards India, USD $8,000). He also received income from Asia Ventilation Forum (workshop/symposium speaker - Covidien paid honoraria). Travel/accommodations were reimbursed by Edwards India; AstraZeneca India and MSD India. His non-financial involvement includes being a board member of the Asia Ventilation Forum (AVF is a working group to enhance ventilatory management in Asian countries).

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). In addition, he has a pending patent for a bed backrest elevation monitor.

Dr. Fujishima disclosed any potential conflicts of interest.

Dr. Gando received grant support for Grants-in-Aid for Science Research from the Ministry of Education, Science, Sports, and Culture in Japan (Grant # 2007-19390456). 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. Gerlach 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).Gerlach disclosed that he has no potential conflicts of interest.

Dr. Goodyear-Bruch disclosed that she has no potential conflicts of interest.

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

Dr. Hazelzet received travel/accommodations reimbursement from ESPNIC and EMEA (EC or expert meeting). He is the Medical President of ESPNIC, and is a member of the European Pediatric Genetic Study consortium.

Dr. Hirasawa reports income to his institution from the Surviving Sepsis Campaign Guideline Committee ($10,000-$25,000). He received honoraria from the Surviving Sepsis Campaign Guideline Committee ($1,000-$5,000). He is the senior author of a manuscript describing the efficacy of continuous hemodiafiltration with cytokine-absorbing hemofilter on sepsis mediator removal.

Dr.Hollenberg consulted for Eisai (Eritoran).

Dr. Jacobi reports grant support to her institution from Eli Lilly (Project Mercury-experience with DAA and an unrestricted educational grant 2009: $1,000-$5,000). She reports income to her institution for the development of educational presentations including service on speakers' bureaus (Eli Lilly 2001-2006; CareFusion Center for Clinical Safety (2007)). Travel/accommodations reimbursed to her institution from Eli Lilly's Speaker's Bureau (SCCM travel-until 2006). She and her husband own stock in healthcare companies, (managed by a broker): Abbott Labs (No sepsis-specific related products); Cardinal Health (distributor of products only - no sepsis therapies of their own); Baxter International (150 shares ~ $8,000-fluids used for resuscitation- may be used in sepsis patients); Edwards Life Sciences (30 shares ~ $2,500 - monitoring devices used in sepsis patients); Merck Medco (no sepsis related products); Pfizer (179 shares ~ $3,400 - antimicrobial products used in sepsis patients- no sepsis-specific therapies). She is the past president of the Society of Critical Care Medicine, and chairs the Society of Critical Care Medicine's task force completing the Glycemic Control guidelines. She is a coauthor of the 'Project Mercury' paper (retrospective evaluation of drotrecogin alfa activated that demonstrated a higher risk of bleeding compared with the prior research populations in RCTs).

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

Dr. Jenkins received income for speakers' bureau activities related to DVT prevention from Medavera and Haymarket Medical Education and Quintiles. He is an author of a sepsis review article (published in the *Journal of Hospital Medicine*, 2006).

Dr. Jimenez received grants paid to his institution from CareFusion (mechanical ventilation research); KCI (abdominal compartment syndrome device research); and Hamilton (mechanical ventilation research). He received income from CareFusion (mechanical ventilation talks related to ongoing research); and KCI (moderator of kinetic therapy symposium). Travel/accommodations reimbursement from CareFusion (travel expenses while giving talks/workshops overseas).

Dr. Jones received grant support from HTI. He is an elected board member of SAEM and EMF. In addition he is the primary author on a manuscript comparing lactate clearance with central venous oxygen saturation.

Dr. Kacmarek is the author of original research papers, editorials and chapters showing the benefit of lung protective ventilation.

Dr. Kern consulted for Pfizer and received grant support paid to his institution from Pfizer. He received honoraria from Pfizer; Janssen-Cilag; Astrellas; and Novartis. Travel/accommodations reimbursed by Bayer.

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-yr R01 grant, PI and 3-yr foundation grant, Co-l). 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; American Association of Critical Care Nurses (one night hotel coverage at national conference).

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

Dr. Kotani reports grant support paid to his institution from AstraZeneca, Asahi Kasei Pharma; EBMs; Kaken Pharmaceutical; Nihon Pharmaceutical; Teijin Pharma Limited; CSL Behring; Torii Pharmaceutical; Mitsubishi Tanabe Pharma; Pfizer Japan Inc.; Daiichi Sankyo, Benesis, Mochida Pharmaceutical, Terumo, Abbott Japan, Otsuka Pharmaceutical Inc; Ono Pharmaceutical; Shionogi; and Toray Medical.

Dr. Levy reports 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). He has been involved with the Surviving Sepsis Campaign guideline from its beginning.

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

Dr. Marini consulted for GE Healthcare (Scientific Advisory Committee). He reports research grant support was paid to institution from GE Healthcare. In addition, he is the investigator for research studies in pandemic influenza (PI for ongoing study of statins as adjuvant therapy); and antibiotics in acquired infection (PI of RCT of empiric antibiotics vs. placebo for suspected ICU-acquired infection).

Dr. Marshall reports consulting income deposited to university division group practice for work as a Steering Committee member for the PROWESS Shock Study; (Eli Lilly); Steering Committee and Clinical Evaluation Committee; ACCESS Study; (Eisai); Steering Committee member for EUPHRATES study; (Spectral Diagnostics; DMC; Artisan Therapeutics; DMC Leo Pharma). He consulted for Idaho Technologies; Bayer; Roche Diagnostics; Pfizer; Daiichi Sankyo; and Vertex Pharmaceuticals. Travel/accommodations reimbursed by Spectral Diagnostics for travel as a speaker to a meeting in Moscow (bioMerieux meeting in Paris). is the Chair of the Canadian Critical Care Trials Group that has undertaken some of the primary research underlying the SSC guidelines; Chair of the International Forum of Acute Care Trialists, an umbrella organization whose members include a number of investigator-led and run consortia that have published work that has formed the basis for the SSC guidelines. He is also a member and past chair of the International Sepsis Forum (received a stipend while chair). He is the

primary investigator for an ongoing study of statins as adjuvant therapy and is the primary investigator of RCT of empiric antibiotics vs. placebo for suspected ICU- acquired infection.

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

Dr. Mehta reports grant support paid to his institution for a sedation related research grant from Canadian Institutes of Health Research. He received honoraria from Hospira (Advisory Board member, $1,500).

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.

Dr. Muscedere reports grant support to his institution for the VAP knowledge translation study ($10,000-$25,000). He received honoraria from Astellas (advisory board for Doripenem $1,000-$5,000). He was the site investigator for a multicenter study on surfactant for ARDS ($10,000-$25,000) from Pneuma Pharma and was the site investigator for a multicenter study on the treatment of VAP with Tygecycline (ongoing study - no funds received) from Wyeth. He is a contributing author on a systemic review and meta-analysis of PCT use. He as also is the lead author for a systematic review and meta-analysis of subglottic secretion drainage for the prevention of VAP.

Dr. Napolitano consulted as an advisory board member for Wyeth, Pfizer, and Ortho McNeil. She received honoraria from medical educational companies (CME lectures and national meetings). Travel/accommodations were reimbursed by Pfizer, Wyeth, and Ortho McNeil.

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

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 immunoglobin 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 yrs); Eisai ($30,000 for 3 yrs); Astra Zeneca ($30,000 for 1 yr); Aggenix ($30,000 for 1 yr); 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). 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). Additionally, he is also on the Data Safety Monitoring Board for Tetraphase (received US $600 in 2012).

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 [non-industry] grant. Grant awarded to chief investigator from ICNARC). She is a trial clinician for ProMISe.

Dr. Parker provides expert testimony for Amer Cunningham Co (June 2010).

Dr. Parrillo consulted for Artisan, Philips, and Cytosorbents Inc and Sangart DSMB. His institution received grants from the Robert Wood Johnson Foundation (New Jersey Health Initiative: Heart Failure) and the Salem Health and Wellness Foundation. He is board member of the National Heart, Blood and Lung Institute's Heart Failure Network.

Dr. Qiu's institution received grants from Pfizer (US $30,000 for MRSA survey); MSD China (US $10,000 for Candidemia survey in China); and Xian-Janssen Pharmaceutical Ltd (US $8,000 for PK/PD of Itraconazole in severe fungal infection). He received honoraria from Pfizer; MSD China; Eli Lilly; AstraZeneca; and Drager(money paid to his institution). He received travel reimbursement from Pfizer (to attend annual ESICM meeting in 2011) and MSD China (to attend SCCM's 41st Congress).

Dr. Randolph consulted for Eisai Pharmaceuticals and Discovery Labs.

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 honararia 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 (~ US $100,000).

Dr. Rello consulted for Intercell (board member); Pasteur-Sanofi, Polyphor and Roche.. He has received grant support from Intercell and Jansen -Cilag. He also received income from Pfizer (lectures) and Wyeth and Pfizer (development of educational presentations).

Dr. Resende received monetary support from Edwards Life Sciences Brazil (development of educational presentation). He is the primary author of a scientific paper about epidemiology of severe sepsis in the emergency department.

Dr. Rhodes consulted for Eli Lilly- monetary compensation paid to himself as well as his institution (Steering Committee for the PROWESS Shock trial) and LiDCO. Travel/accommodation reimbursement 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, andbelieves in the concept of minimally invasive hemodynamic monitoring.

Dr. Rivers consulted for AstraZeneca ($2,000); bioMerieux ($1,000); Aggenix ($1,500); Idaho Technologies ($1000), Massimo ($1000), Phillips Electronics ($500), Edwards Life Sciences (no money was received); Institute of Medicine, National Academies of Sciences (consulted to the

U.S. Government on health affairs); Eisai Pharma ($1,500). His institution received grant support from Biosite, Inc (biomarkers in sepsis $120,000); Edwards Life Sciences (Inflammation of sepsis $150,000); National Institutes of Health (community-acquired sepsis $500,000); Aggennix-telactoferin in sepsis $50,000); Hutchinsons Technologies (NIRS in the triage of ED patients [co-investigator] $150,000); Innverness (biomarker for renal failure-$90,000 for one year). He received honoraria from Edwards Lifesciences, Elan Pharmaceuticals ($1,500); Merck ($4,000); and Eli Lilly. He owns the rights to a patent for venous oximetry (never received re-numeration or royalties). He is the co-investigator on the following studies: cortisol levels in sepsis; telactoferrin in sepsis; observational study of SSC implementation; procalcitonin in sepsis; and markers of renal failure. Additionally, he is on the Quality and Safety Board for Catholic Health Partners East.

Dr. Rubenfeld received grant support from non-profit 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); Simens ($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, 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.

Ms. Schorr reports travel support from the Society of Critical Care Medicine (Faculty member of SSC Phase III). is a coauthor of a prospective cohort study of 15,022 patients studying an intervention to facilitate compliance with the SSC guidelines (specifically SSC bundle performance improvement). She is the coauthor of a multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis.

Dr. Sevransky reports 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. Shukri disclosed that he has no potential conflicts of interest.

Dr. Silva consulted for MSD ($3,000).

Dr. Soth received honoraria from Wyeth ($2,000 resident review).

Dr. Sprung reports 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 (<$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 also 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. Thompson disclosed that she has no potential conflicts of interest.

Dr. Townsend is an advocate for Healthcare Quality Improvement.

Dr. Vender receives honoraria and consulting income from Edwards Lifesciences and Hospira (lectures on hemodynamic monitoring and for consulting on new technologies).

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. Webb consulted for AstraZeneca (anti-infectives $1,000-$5,000) and Jansen-Cilag (ani-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 versus 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 betalactam 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). Received travel/accommodations reimbursed from 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. Welte consulted for Novartis; MSD; Bayer; AstraZeneca; Astellas; and Pfizer. His institution received grant support from Novartis and Bayer. He received honoraria from Intercell, Pari (Data Monitoring Board), GlaxoSmithKline, Nycomed, Novartis (COPD) and MED Update (Pneumo and ICU Update development).

Dr. Zimmerman disclosed that she has no potential conflicts of interest.

Online Appendix B

Supplemental Bibliography

Observational studies showing improved outcomes with early quantitative resuscitation between 2001-2011

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
2. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. Crit Care 2005;9:R764-70.
3. Sebat F, Johnson D, Musthafa AA, et al. A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. Chest 2005;127:1729-43.
4. Kortgen A, Niederprum P, Bauer M. Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. Crit Care Med 2006;34:943-9.
5. Shapiro NI, Howell MD, Talmor D, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. Crit Care Med 2006;34:1025-32.
6. Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. Chest 2006;129:225-32.
7. Micek ST, Roubinian N, Heuring T, et al. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 2006;34:2707-13.
8. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 2006;26:551-7.
9. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med 2007;35:1105-12.
10. Jones AE, Focht A, Horton JM, Kline JA. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. Chest 2007;132:425-32.
11. El Solh AA, Akinnusi ME, Alsawalha LN, Pineda LA. Outcome of septic shock in older adults after implementation of the sepsis "bundle". J Am Geriatr Soc 2008;56:272-8.
12. Castro R, Regueira T, Aguirre ML, et al. An evidence-based resuscitation algorithm applied from the emergency room to the ICU improves survival of severe septic shock. Minerva Anestesiol 2008;74:223-31.
13. Zambon M, Ceola M, Almeida-de-Castro R, Gullo A, Vincent JL. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster. J Crit Care 2008;23:455-60.
14. Zubrow MT, Sweeney TA, Fulda GJ, et al. Improving care of the sepsis patient. Jt Comm J Qual Patient Saf 2008;34:187-91.

15. Focht A, Jones AE, Lowe TJ. Early goal-directed therapy: improving mortality and morbidity of sepsis in the emergency department. Jt Comm J Qual Patient Saf 2009;35:186-91.
16. Puskarich MA, Marchick MR, Kline JA, Steuerwald MT, Jones AE. One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study. Crit Care 2009;13:R167.
17. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. Jama 2008;299:2294-303.
18. Girardis M, Rinaldi L, Donno L, et al. Effects on management and outcome of severe sepsis and septic shock patients admitted to the intensive care unit after implementation of a sepsis program: a pilot study. Crit Care 2009;13:R143.
19. Wang JL, Chin CS, Chang MC, et al. Key process indicators of mortality in the implementation of protocol-driven therapy for severe sepsis. J Formos Med Assoc 2009;108:778-87.
20. Pestana D, Espinosa E, Sanguesa-Molina JR, et al. Compliance with a sepsis bundle and its effect on intensive care unit mortality in surgical septic shock patients. J Trauma 2010.
21. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, et al. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Crit Care Med 2010;38:1036-43.
22. Lefrant JY, Muller L, Raillard A, et al. Reduction of the severe sepsis or septic shock associated mortality by reinforcement of the recommendations bundle: A multicenter study. Ann Fr Anesth Reanim 2010.
23. Cardoso T, Carneiro AH, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A. Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese community-acquired sepsis study (SACiUCI study). Crit Care 2010;14:R83.
24. Crowe CA, Mistry CD, Rzechula K, Kulstad CE. Evaluation of a modified early goal-directed therapy protocol. Am J Emerg Med 2010;28:689-93.
25. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J 2011;28:507-12.
26. Gurnani PK, Patel GP, Crank CW, et al. Impact of the implementation of a sepsis protocol for the management of fluid-refractory septic shock: a single-center, before-and-after study. Clin Ther 2010;32:1285-93.
27. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Critical Care Medicine 2010;38:367-74.
28. Macredmond R, Hollohan K, Stenstrom R, Nebre R, Jaswal D, Dodek P. Introduction of a comprehensive management protocol for severe sepsis is associated with sustained improvements in timeliness of care and survival. Qual Saf Health Care 2010.
29. Coba V, Whitmill M, Mooney R, et al. Resuscitation bundle compliance in severe sepsis and septic shock: improves survival, is better late than never. J Intensive Care Med 2011.
30. Sivayoham N, Rhodes A, Jaiganesh T, van Zyl Smit N, Elkhodhair S, Krishnanandan S. Outcomes from implementing early goal-directed therapy for severe sepsis and septic shock : a 4-year observational cohort study. Eur J Emerg Med 2011.

31. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Ortiz F, Llorca J, Delgado-Rodriguez M. Late compliance with the sepsis resuscitation bundle: impact on mortality. Shock 2011;36:542-7.
32. Schramm GE, Kashyap R, Mullon JJ, Gajic O, Afessa B. Septic shock: A multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality. Crit Care Med 2011;39:252-8.
33. Nguyen HB, Kuan WS, Batech M, et al. Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. Crit Care 2011;15:R229.
34. Shiramizo SC, Marra AR, Durao MS, Paes AT, Edmond MB, Pavao dos Santos OF. Decreasing mortality in severe sepsis and septic shock patients by implementing a sepsis bundle in a hospital setting. PLoS ONE 2011;6:e26790.
35. Tromp M, Tjan DH, van Zanten AR, et al. The effects of implementation of the Surviving Sepsis Campaign in the Netherlands. Neth J Med 2011;69:292-8.

Combined topical digestive tract antibiotics (includes chlorhexidine) versus no prophylaxis for mechanical ventilation > 48 hours

Patients: Adults intubated > 48 hours
Settings: Intensive care unit
Intervention: Topical digestive tract antimicrobials, including chlorhexidine
Comparison: No prophylaxis
Sources: Analysis performed by Mark Nunnally and Steve Opal for Surviving Sepsis Campaign, using following publications: Liberati A. Cochrane Database of Systematic Reviews 2010 Issue 9; de Smet AMGA. NEJM 2009;360(1):20-3; Chan E. BMJ 2007;334:889-900; Bellisimo-Rodrigues F. Infect Control Hosp Epidemiol 2009;30(10):952-58; Cabov T. Wien Klin Wochenschr 2010;122:397-404; Panchabhai TS. Chest 2009;135:1150-56; Scannapieco FA. Crit Care 2009;13(4):R117;Tantipong H. Infect Control Hosp Epidemiol 2008;29(2):131-6.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Topical antimicrobials				
Overall mortality, all studies	**269 per 1000**	**266 per 1000** (250 to 285)	**RR 0.99** (0.93 to 1.06)	8530 (25 studies)	⊕⊕⊕⊖ **moderate**[1,2,3]	
Overall mortality - chlorhexidine v no prophylaxis	**178 per 1000**	**188 per 1000** (164 to 215)	**RR 1.06** (0.92 to 1.21)	2853 (11 studies)	⊕⊕⊕⊖ **moderate**[2,3,4]	
Overall mortality - topical antibiotics v no prophylaxis	**313 per 1000**	**303 per 1000** (281 to 328)	**RR 0.97** (0.9 to 1.05)	5677 (14 studies)	⊕⊕⊕⊖ **moderate**[2,3,5]	
Respiratory tract infection all studies	**221 per 1000**	**124 per 1000** (99 to 152)	**RR 0.56** (0.45 to 0.69)	4588 (23 studies)	⊕⊕⊕⊖ **moderate**[2,6]	
Respiratory tract infection - Chlorhexidine v no prophylaxis	**156 per 1000**	**100 per 1000** (80 to 127)	**RR 0.64** (0.51 to 0.81)	2853 (11 studies)	⊕⊕⊕⊖ **moderate**[2,7]	
Respiratory tract infection - Topical antibiotic v no prophylaxis	**321 per 1000**	**154 per 1000** (106 to 218)	**RR 0.48** (0.33 to 0.68)	1735 (12 studies)	⊕⊕⊕⊖ **moderate**[2,8]	

*The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) 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

[1] I squared = 0%; test for subgroup differences, I squared = 15%.
[2] Patient population includes all critically ill patients, not just septic patients.
[3] Several studies suggest harm, but we did not lower the quality of evidence for imprecision.
[4] I squared = 11% (p = 0.34).
[5] I squared = 0%.
[6] I squared = 52% (p = 0.002). Test for subgroup differences, I squared = 46.6% (p = 0.17). We did not lower for heterogeneity, because the issue is only the degree of benefit.
[7] I squared = 20% (p = 0.26).
[8] I squared = 68% (p = 0.0003). We did not lower for heterogeneity, because the issue is only the degree of benefit.

Online Appendix D

Low dose long term glucocorticosteroids for severe sepsis and septic shock

Patient or population: Patients with severe sepsis and septic shock
Settings: Intensive care unit
Intervention: Low dose long term glucocorticosteroids
Comparison: No corticosteroid
Sources: Analysis performed by Herwig Gerlach for the Surviving Sepsis Campaign, using following publication: Patel GP. Am J Respir Crit Care Med 2012;185:133-9.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**Low dose long term glucocorticosteroids**				
Mortality Follow-up: mean 28 days	**432 per 1000**	**394 per 1000** (329 to 467)	**RR 0.91** (0.76 to 1.08)	968 (6 studies)	⊕⊕⊖⊖ **low**[1,2]	
Mortality in higher baseline mortality studies Follow-up: mean 28 days	**612 per 1000**	**471 per 1000** (343 to 642)	**RR 0.77** (0.56 to 1.05)	381 (3 studies)	⊕⊕⊕⊖ **moderate**[3,4]	
Mortality in lower baseline mortality studies Follow-up: mean 28 days	**317 per 1000**	**336 per 1000** (270 to 425)	**RR 1.06** (0.85 to 1.34)	587 (3 studies)	⊕⊕⊕⊖ **moderate**[5]	

*The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) 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

[1] Some suggestion of heterogeneity between 3 studies with higher baseline mortality and 3 with lower.
[2] Results are not statistically significant and include large benefit and small harm.
[3] I squared 31%, but concerns size of benefit and not direction.
[4] Imprecision. With the use of fixed effect model RR 0.82 (0.69-0.99).
[5] Imprecision as confidence intervals include harm.

Online Appendix E

Neuromuscular blocking agents (NMBA) compared to Placebo in patients with Acute Respiratory Distress Syndrome (ARDS).

Patient or population: Patients with ARDS
Settings: Intensive care unit (ICU)
Intervention: NMBA
Comparison: Placebo
Sources: Analysis performed by Alhazzani, W and Sevransky, J for the Surviving Sepsis Campaign, using following publications: Papazian L. NEJM 2010;363:1107-16; Gainnier M. Crit Care Med 2004;32:113-9; and Forel JM. Crit Care Med 2006;34:2749-57.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	**NMBA**				
Mortality at 28 days	**Study population**		**RR 0.66** (0.50 to 0.87)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	389 per 1000	**257 per 1000** (195 to 339)				
Mortality in the ICU	**447 per 1000**	**313 per 1000** (246 to 398)	**RR 0.70** (0.55 to 0.89)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Ventilator Free Days Follow-up: 28 days		The mean ventilator free days in the intervention groups was **1.91 higher** (0.28 to 3.55 higher)		431 (3 studies)	⊕⊕⊕⊕ **high**[3]	
ICU acquired weakness	**298 per 1000**	**322 per 1000** (247 to 420)	**RR 1.08** (0.83 to 1.41)	431 (3 studies)	⊕⊕⊖⊖ **low**[1,2,4]	
Barotrauma	**96 per 1000**	**41 per 1000** (19 to 87)	**RR 0.43** (0.20 to 0.90)	431 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	

*The **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) 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

[1] Two trials lacked appropriate blinding.
[2] Due to small number of available trials we could not assess for publication bias.
[3] Ventilator Free Days correlate with survival.
[4] Wide confidence interval crossing equivalence and including significant harm.

Online Appendix F

Histamine-2 receptor antagonists (H2RA) compared to placebo or no treatment for prevention of GI bleeding

Patient or population: Critically ill patients
Settings: Intentsive care units
Intervention: H2RA
Comparison: Placebo or no treatment
Source: Prepared by Alhazzani, W and Sprung, C for the Surviving Sepsis Campaign using the following studies: Marik PE. Crit Care Med 2010;38:2222-8; Leonard J . Am J Gastroenterol 2007;102:2047-56.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk H2RA				
Clinically important GI bleeding (CIB)	**Low**[1]		**Odds Ratio (OR) 0.47** (0.29 to 0.76)	1836 (17 studies)	⊕⊕⊕⊖ **moderate**[2,3,4]	
	5 per 1000	**2 per 1000** (1 to 4)				
	High[1]					
	50 per 1000	**24 per 1000** (15 to 38)				
Overall mortality	**164 per 1000**	**168 per 1000** (132 to 211)	**OR 1.03** (0.78 to 1.37)	1540 (14 studies)	⊕⊕⊕⊖ **moderate**[4,5]	
Nosocomial (hospital acquired) pneumonia	**114 per 1000**	**165 per 1000** (103 to 252)	**OR 1.53** (0.89 to 2.61)	1157 (9 studies)	⊕⊕⊕⊖ **moderate**[4,6]	
Clostridium difficile infection (in studies examining any antisecretory therapy[7])	**50 per 1000**	**93 per 1000** (72 to 120)	**OR 1.95** (1.48 to 2.58)	18468 (19 studies)	⊕⊖⊖⊖ **very low**[7]	

[1] Frequency of clinically important GI bleeding varies (1.5% (observational study, Cook NEJM 1994;330:377), 3.8% (group receiving sucralfate in Cook NEJM 1998,338:791)). In the first study patients without need for mechanical ventilation for >48h and without coagulopathy (platelet count <50,000 or INR>1.5 or APTT>2 times normal) had 0.1% risk of bleeding. Other authors list number of other potential risk factors of less established significance including burn, brain or multiple trauma, hypotension, renal or liver failure, steroid use, etc.
[2] All studies used randomization, most used blinding. Quality of evidence not lowered.
[3] Benefits not present in studies using enteral nutrition for all or most of the patients (OR for mortality 1.89 (1.04-3.44, total of 65 events)); for pneumonia OR 2.81 (1.2-6.56, 41 events) and for CIB 1.26 (0.43-3.7, 28 events). We consider this an exploratory finding and, while lowering the quality of evidence, decided to provide one recommendation. We acknowledge the possibility of a different interpretation.
[4] Most studies are old, and may be of limited applicability today. Quality of Evidence not lowered.
[5] Overall no difference, possible harm in studies using enteral nutrition.
[6] Unable to exclude harm.
[7] From Leonard J, et al. Am J Gastroenterol 2007;102: 2047. Observational studies with indirectness to critically ill patients. The association was numerically greater for PPI (OR 2.05 (1.47-2.85)) than for H2RA (OR 1.48 (1.06-2.06)) without statistically significant difference between those two classes of drugs (p=0.17). We did not consider this outcome critical, but we acknowledge the possibility of a different interpretation.

Online Appendix G

Proton Pump Inhibitors (PPI) compared to Histamine-2 receptor antagonists (H2RA) for prevention of GI bleeding

Patient or population: Critically ill patients
Settings: Intensive care units
Intervention: PPI
Comparison: H2RA
Sources: Prepared by Alhazzani, W and Sprung, C for the Surviving Sepsis Campaign using the following studies: Al-Hazzani. Pol Arch Int Med 2012. Leonard J. Am J Gastroent 2007102:2047-56.

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **H2RA**	Corresponding risk **Proton Pump Inhibitors (PPI)**				
Clinically important GI bleeding	**Low**		**Relative Risk (RR) 0.36** (0.19 to 0.67)[1]	1274 (11 studies)	⊕⊕⊖⊖ **low**[2,3,4]	
	10 per 1000	**4 per 1000** (2 to 7)				
	High					
	50 per 1000	**18 per 1000** (10 to 34)				
Overall mortality	**223 per 1000**	**223 per 1000** (181 to 275)	**RR 1.00** (0.81 to 1.23)	1007 (7 studies)	⊕⊕⊕⊖ **moderate**[5]	
Nosocomial pneumonia	**105 per 1000**	**112 per 1000** (77 to 160)	**RR 1.06** (0.73 to 1.52)[6]	1100 (8 studies)	⊕⊕⊕⊖ **moderate**[2,7]	
Clostridium difficile infection (in studies examining any antisecretory therapy)	**50 per 1000**	**93 per 1000** (72 to 120)	**Odds Ratio (OR) 1.95** (1.48 to 2.58)	18468 (19 studies)	⊕⊖⊖⊖[8] **very low**	

[1] In two recent meta-analyses (Pongprasobchai. J Med Assoc Thai 2009;92:632; Lin. Crit Care Med 2010;38:1197): OR 0.42 (95% CI 0.2-0.91) and Risk Difference (RD) -4% (95% CI -9 to +1%).
[2] Only 3 studies were in low bias risk category. For the remainder, the bias risk was mostly due to unclear blinding and unclear concealment of randomization. This is less important for mortality (not downgraded for that outcome).
[3] High or unknown risk of bias studies (lower quality) provided larger estimate of PPI efficacy than studies of higher quality (RR 0.16 (0.07-0.39)) versus 0.6 (0.27-1.35).
[4] Some asymmetry noted; quality of evidence is not lowered.
[5] A minority of the studies was in the low bias risk category. Most studies had unclear blinding and concealment of randomization.
[6] Two recent meta-analyses (Pongprasobchai 2009; Lin 2010): RD +1% (-9 to +11%), OR 1.02 (0.59-1.75).
[7] Imprecision: Wide confidence interval.
[8] From Leonard J, et al. Am J Gastroenterol 2007;102: 2047. Observational studies with indirectness to critically ill patientsThe association was numerically greater for PPI (OR 2.05 (1.47-2.85)) than for H2RA (OR 1.48 (1.06-2.06)) without statistically significant difference between those two classes of drugs (p=0.17). We did not consider this outcome critical, but we acknowledge the possibility of a different interpretation.

Online Appendix H

Figure 1: Mortality in Clinical Trials of Intensive Insulin Therapy by High or Moderate Control Groups