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SPECIAL ARTICLE

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

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Abstract *Objective:* To develop management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis. *Design:* The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. The modified Delphi methodology used for grading recommendations built upon a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along 5 levels to create recommendation grades from A–E, with A being the highest grade. Pediatric considerations were provided to contrast adult and pediatric management. *Participants:* Participants included 44 critical care and infectious disease experts representing 11 international organizations. *Results:* A total of 46 recommendations plus pediatric management considerations. *Conclusions:* Evidence-based recommendations can be made regarding many aspects of the acute management of sepsis and septic shock that will hopefully translate into improved outcomes for the critically ill patient. The impact of these guidelines will be formally tested and guidelines updated annually, and even more rapidly when some important new knowledge becomes available.

Keywords Sepsis · Severe sepsis · Septic shock · Sepsis syndrome · Infection · Guidelines · Evidence-based medicine · Surviving Sepsis Campaign

Introduction

The mortality of severe sepsis (infection-induced organ dysfunction or hypoperfusion abnormalities) and septic shock (hypotension not reversed with fluid resuscitation and associated with organ dysfunction or hypoperfusion abnormalities) in most centers remains unacceptably high [1, 2]. Similar to an acute myocardial ischemic attack and an acute brain attack, the speed and appropriateness of therapy administered in the initial hours after the syndrome develops are likely to influence outcome. A group of international critical care and infectious disease experts in the diagnosis and management of infection and sepsis, representing 11 organizations, came together to develop guidelines that the bedside clinician could use to improve outcome in severe sepsis and septic shock. This process represented phase II of the Surviving Sepsis Campaign (SSC), an international effort to increase awareness and improve outcome in severe sepsis. The full committee meeting expenses as well as staff support for guidelines creation were provided by unrestricted industry educational grants as listed. There were no industry members on the committee. There was no industry input into guidelines development and no industry presence at any of the meetings of the committee or subgroups of the committee. Industry awareness or comment on the recommendations was not allowed. The industries did not see the recommendations until the manuscript was peer-reviewed and accepted for publication in its final form. Phase I of the SSC was initiated in October of 2002 with the Barcelona Declaration to improve survival in severe sepsis, and phase III will be dedicated to the use of the management guidelines to evaluate the impact on clinical outcome. A comprehensive document created from the deliberations of the committee will be submitted for publication as a supplement. This document represents an executive summary of the consensus process with presentation of key recommendations. These recommendations are intended to provide guidance for the clinician caring for a patient with severe sepsis or septic shock, but they are not applicable for all patients. Recommendations from these guidelines cannot replace the clinician's decision-making capability when he or she is provided with a patient's unique set of clinical variables.

Although these recommendations are written primarily for the patient in the intensive care unit (ICU) setting, many recommendations are appropriate targets for the pre-ICU setting. It should also be noted that resource limitations may prevent physicians from accomplishing a recommendation.

Methods

The recommendations are graded based on a modified Delphi methodology with categorization as previously described (Table 1) [3]. The methods for this document build upon a 2001 publication

Table 1 Grading system

Grading recommendations	
A.	Supported by at least 2 level I investigations
B.	Supported by 1 level I investigation
C.	Supported by level II investigations only
D.	Supported by at least 1 level III investigation
E.	Supported by level IV or V evidence
Grading of evidence	
I.	Large, randomized trials with clearcut results; low risk of false-positive (alpha) error or false-negative (beta) error
II.	Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III.	Non-randomized, contemporaneous controls
IV.	Non-randomized, historical controls and expert opinion
V.	Case series, uncontrolled studies, and expert opinion

sponsored by the International Sepsis Forum, and use the same method of recommendation grading [4]. The grading system was applied to the question from which each recommendation is created. The supplement submission includes background material, questions, and expanded rationale. This executive summary is targeted to be concise and user friendly for the bedside clinician. The 2001 publication which represented a starting point for the current process, included a MEDLINE search for clinical trials in the preceding 10 years, supplemented by a manual search of other relevant journals. Subtopics for each recommendation were cross-referenced to sepsis, severe sepsis, septic shock, sepsis syndrome, and infection. The SSC guidelines considered the evidence in the 2001 publication (through 1999) and repeated the process for 2000 through 2003. The consensus committee met in June 2003 with the first presentations of data and recommendations. At that time, recommendations were discussed and critiqued. Each clinical trial used to support recommendations was graded based on the methodology in Table 1 and included presence or absence of important elements such as concealed randomization, blinded outcome adjudication, intention to treat analysis, and explicit definition of primary outcome. All articles were initially reviewed based on subgroup assignments and typically by 2–3 participants. Survival (28–30 days) was the standard outcome measure used to assess outcome benefit and when an alternative was used this is stated in the rationale. Where strong trial based evidence existed for outcome benefit in critically ill populations known to contain a large number of sepsis patients, these trials were considered in determination of recommendation grading. A strict evidence-based methodology was not used, for example a scoring system was not used. The goal was total consensus which was reached in all recommendations except two. In those two circumstances (recommendations C.3 and H.1) the solution was achieved with subrecommendations that expressed some differences in expert opinion.When there was difference of opinion about grading of a clinical trial, an outside epidemiologist was consulted. This occurred in one circumstance with resolution of differences. Each participant completed a conflict of interest form that was made available at the meeting. Individuals were not assigned to a subgroup topic where they had a potential conflict of interest. A full listing of all potential conflicts of interest are included with this manuscript. Following that meeting, the process continued with further refinements of recommendations through electronic communication among committee members. A second meeting of core members of the committee occurred in early October of 2003. The document was finalized and approved by the consensus committee and by sponsoring organizations in December 2003.

Evidence-based approaches are more readily applied to data from therapeutic trials. Evaluation of diagnostic techniques is less well suited to this approach. Readers will note that the majority of the recommendations are not supported by high-level evidence. Most are supported by expert opinion only. In order for a general recommendation to carry a higher level of evidence (Grades A, B, C, or D), a supporting study or studies must have shown a clinical outcome difference. Studies showing physiologic changes that could be potential surrogates of clinical outcome benefit were not used by themselves as pivotal studies, but were used to support the validity of studies showing an outcome in a clinically important parameter such as survival or length of intensive care unit (ICU) stay. A grade of A, B, or C required randomized trials. Recommendations are graded and followed with the rationale. References are provided to support grades A–D. In the committee's deliberations, the grading of a recommendation did not establish the level of priority or importance of a specific intervention, only the degree of literature support. Pediatric considerations are provided at the end of the document for aspects of management that differ from adults. Recommendations are grouped by category and not by hierarchy.

A. Initial resuscitation

1. The resuscitation of a patient in severe sepsis or sepsis-induced tissue hypoperfusion (hypotension or lactic acidosis) should begin as soon as the syndrome is recognized and should not be delayed pending ICU admission. An elevated serum lactate level identifies tissue hypoperfusion in patients at risk who are not hypotensive. During the first 6 h of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

- Central venous pressure (CVP) 8–12 mmHg
- Mean arterial pressure (MAP) $\geq$65 mmHg
- Urine output $\geq$0.5 ml/kg h^{-1}
- Central venous (superior vena cava) or mixed venous oxygen saturation $\geq$70%.

Grade B.

Rationale. Early goal-directed therapy (EGDT) has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single center study [5]. Resuscitation directed toward the above goals for the initial 6 h period of the resuscitation was able to reduce 28-day mortality. The consensus panel judged central venous and mixed venous oxygen saturation to be equivalent. Either intermittent or continuous measurements of O_2 saturation are judged to be acceptable. Although lactate measurement may be useful, it lacks precision as a measure of tissue metabolic status. In mechanically ventilated patients a higher target CVP of 12–15 mmHg is recommended to account for the increased intrathoracic pressure. Similar considerations may be given in circumstances of increased abdominal pressure. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated

pulse with fluid resuscitation is often a useful marker or improving intravascular filling.

2. During the first 6 h of resuscitation of severe sepsis or septic shock, if $ScvO_2$ or SvO_2 of 70% is not achieved with fluid resuscitation to a CVP of 8–12 mmHg, then transfuse packed red blood cells to achieve an hematocrit of 30% or greater and/or administer a dobutamine infusion (up to a maximum of 20 μg/kg/min) to achieve this goal.

Grade B.

Rationale. The protocol used in the study cited above targeted an increase in SvO_2 to $\geq$70%. This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival [5].

B. Diagnosis

1. Appropriate cultures should always be obtained before antimicrobial therapy is initiated. In order to optimize identification of causative organisms, at least 2 blood cultures should be obtained with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 h) inserted. Cultures of other sites such as urine, cerebrospinal fluid, wounds, respiratory secretions or other body fluids should be obtained before antibiotic therapy is initiated as the clinical situation dictates.

Grade D.

Rationale. Two or more blood cultures are recommended [6]. Ideally at least one blood culture should be drawn through each lumen of each vascular access device. Obtaining blood cultures peripherally and through a vascular access device is an important strategy. If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e., more than 2 h earlier, it may offer support that the vascular access device is the source of the infection [7]. Volume of blood may also be important [8].

2. Diagnostic studies should be performed promptly to determine the source of the infection and the causative organism. Imaging studies and sampling of likely sources of infection should be performed; however, some patients may be too unstable to warrant certain invasive procedures or transport outside of the ICU. Bedside studies, such as ultrasound, may be useful in these circumstances.

Grade E.

Rationale. Diagnostic studies may identify a source of infection that must be drained in order to maximize the likelihood of a satisfactory response to therapy. However, even in the most organized and well-staffed health care facilities, transport of patients can be dangerous, as can placing patients in outside-unit imaging devices that are difficult to access and monitor.

C. Antibiotic therapy

1. Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.

Grade E.

Rationale. Establishing vascular access and initiating aggressive fluid resuscitation is the first priority when managing patients with severe sepsis or septic shock. However, prompt infusion of antimicrobial agents is also a logical strategy, and may require additional vascular access ports. Establishing a supply of pre-mixed antibiotics in an emergency department or critical care unit for such urgent situations is an appropriate strategy for enhancing the likelihood that antimicrobial agents will be infused promptly. Staff should be cognizant that some agents require more lengthy infusion time whereas others can be rapidly infused or even administered as a bolus.

2. Initial empiric anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and which penetrate into the presumed source of sepsis. The choice of drugs should be guided by the susceptibility patterns of microorganisms in the community and in the hospital.

Grade D.

Rationale. The choice of empiric antibiotics depends on complex issues related to the patient's history (including drug intolerance), underlying disease, the clinical syndrome, and susceptibility patterns in the patient's community and in the health care facility.

The initial selection of an empiric antimicrobial regimen should be broad enough, according to the above criteria, covering all likely pathogens since there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the causative pathogen) has adverse consequences on outcome [9, 10, 11, 12].

While restricting the use of antibiotics, and particularly broad-spectrum antibiotics, is important for limiting superinfection and for decreasing the development of antibiotic-resistant pathogens, patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antibiotic susceptibilities are defined. At that point, restriction of the number of antibiotics and narrowing the spectrum of antimicrobial therapy is an important and responsible strategy for

minimizing the development of resistant pathogens and for containing costs.

All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. The ICU pharmacist should be consulted to assure that serum concentrations are attained which maximize efficacy and minimize toxicity [13, 14, 15, 16].

3. The antimicrobial regimen should always be reassessed after 48 to 72 h on the basis of microbiological and clinical data with the aim of using a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs. Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy. The duration of therapy should typically be 7 to 10 days and guided by clinical response.

Grade E.

a. Some experts prefer combination therapy for patients with *Pseudomonas* infections.

Grade E.

b. Most experts would use combination therapy for neutropenic patients with severe sepsis or septic shock. For neutropenic patients, broad-spectrum therapy usually must be continued for the duration of the neutropenia.

Grade E.

Rationale. Use of antimicrobial agents with a more narrow spectrum and reducing the duration of therapy will reduce the likelihood that the patient will develop superinfection with pathogenic or resistant organisms such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*. However, the desire to minimize superinfections and other complications should not take precedence over the need to give the patient an adequate course of potent antimicrobials.

4. If the presenting clinical syndrome is determined to be due to a non-infectious cause, antimicrobial therapy should be stopped promptly to minimize the development of resistant pathogens and superinfection with other pathogenic organisms.

Grade E.

Rationale. Clinicians should be cognizant that blood cultures will be negative in the majority of cases of sepsis or septic shock. Thus, the decision to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and other culture results.

D. Source control

1. Every patient presenting with severe sepsis should be evaluated for the presence of a focus of infection amenable to source control measures, specifically the drainage of an abscess or local focus of infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination [17]. (See appendix A for examples of potential sites needing source control.)

Grade E.

Rationale. Health care professionals should engage specialists in other disciplines such as radiology, surgery, pulmonary medicine, and gastroenterology to obtain diagnostic samples and to drain, debride, or remove the infection source as appropriate.

2. The selection of optimal source control methods must weigh benefits and risks of the specific intervention. Source control interventions may cause further complications such as bleeding, fistulae, or inadvertent organ injury; in general the intervention that accomplishes the source control objective with the least physiologic upset should be employed, e.g., consideration of percutaneous rather than surgical drainage of an abscess [18].

Grade E.

3. When a focus of infection amenable to source control measures such as an intra-abdominal abscess, a gastrointestinal perforation, cholangitis, or intestinal ischemia has been identified as the cause of severe sepsis or septic shock, source control measures should be instituted as soon as possible following initial resuscitation.

Grade E.

Rationale. Case series and expert opinion support the principle that rapid correction of a source of microbial contamination is essential to maximize survival of the severely septic patient with acute physiologic deterioration. Intervention should only be undertaken following adequate resuscitation. Timely and emergent intervention is particularly important for patients with necrotizing soft tissue infection or intestinal ischemia [19].

4. If intravascular access devices are potentially the source of severe sepsis or septic shock, they should be promptly removed after establishing other vascular access.

Grade E.

Rationale. Intravascular access devices are thought to be the source of the majority of nosocomial blood stream infections. When patients develop sepsis of unknown source, it may be reasonable to leave vascular access devices in place until the source of infection can be determined. However, when patients have severe sepsis or septic shock of unknown source, clinicians should consider removal and replacement of vascular access devices to be a priority, even if the device is tunneled or surgically implanted [20, 21].

E. Fluid therapy

See initial resuscitation recommendations (A1–2) for timing of resuscitation.

1. Fluid resuscitation may consist of natural or artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another.

Grade C.

Rationale. Although prospective studies of choice of fluid resuscitation in patients with septic shock only are lacking, meta-analysis of clinical studies comparing crystalloid and colloid resuscitation in general and surgical patient populations indicate no clinical outcome difference between colloids and crystalloids and would appear to be generalizable to sepsis populations [22, 23, 24]. As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end-points and results in more edema.

2. Fluid challenge in patients with suspected hypovolemia (suspected inadequate arterial circulation) may be given at a rate of 500–1000 ml of crystalloids or 300–500 ml of colloids over 30 min and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload).

Grade E.

Rationale. Fluid challenge must be clearly separated from an increase in maintenance fluid administration. Fluid challenge is a term used to describe the initial volume expansion period in which the response of the patient to fluid administration is carefully evaluated. During this process large amounts of fluids may be administered over a short period of time under close monitoring to evaluate the patient's response and avoid the development of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With vasodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 h of management. Input (I) is typically much greater than output (O), and I/O ratio is of no utility to judge fluid resuscitation needs during this time period.

F. Vasopressors

1. When an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when a fluid challenge is in progress and hypovolemia has not yet been corrected.

Grade E.

Rationale. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow. It is important to supplement goals such as blood pressure with assessment of global perfusion such as blood lactate concentrations. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors are used, but it is frequently necessary to employ vasopressors early as an emergency measure in patients with severe shock [25, 26].

2. Either norepinephrine or dopamine (through a central line as soon as available) is the first-choice vasopressor agent to correct hypotension in septic shock.

Grade D.

Rationale. Although there is no high-quality primary evidence to recommend one catecholamine over another, human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (potential tachycardia, possibly disadvantageous effects on splanchnic circulation) and phenylephrine (decrease in stroke volume). Phenylephrine is the adrenergic agent least likely to produce tachycardia. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared to dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic [25, 27, 28, 29, 30]

3. Low-dose dopamine should not be used for renal protection as part of the treatment of severe sepsis.

Grade B.

Rationale. A large randomized trial and a meta-analysis comparing low-dose dopamine to placebo in critically ill patients found no difference in either primary outcomes (peak serum creatinine, need for renal replacement therapy, urine output, time to recovery of normal renal function), or secondary outcomes (survival to either ICU or hospital discharge, ICU stay, hospital stay, arrhythmias). Thus the available data do not support administration of low doses of dopamine to maintain or improve renal function [31, 32].

4. All patients requiring vasopressors should have an arterial catheter placed as soon as practical if resources are available.

Grade E.

Rationale. In shock states, measurement of blood pressure using a cuff is commonly inaccurate, whereas use of an arterial catheter provides a more accurate and reproducible measurement of arterial pressure. Monitoring using these catheters also allows beat-to-beat analysis so that decisions regarding therapy can be based on immediate blood pressure information [25]. Placement of an arterial line in the emergency department is typically not possible or practical. It is important to appreciate the complications of arterial line placement which include hemorrhage and damage to arterial vessels.

5. Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first line agent. If used in adults, it should be administered at infusion rates of 0.01–0.04 U/min. It may decrease stroke volume.

Grade E.

Rationale. Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors, although no outcome data are available. Unlike dopamine and epinephrine, vasopressin is a direct vasoconstrictor without inotropic or chronotropic effects and may result in decreased cardiac output and hepatosplanchnic flow. Most published reports exclude patients from treatment with vasopressin if the cardiac index is less than 2 or 2.5 l/min m^{-2} and it should be used with caution in patients with cardiac dysfunction. Studies show that vasopressin levels are elevated in early septic shock, but with continued shock, levels drop to normal range in the majority of patients between 24 and 48 h [33]. This has been called "relative vasopressin deficiency" since in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. Doses of vasopressin higher than 0.04 U/min have been associated with myocardial ischemia, significant decreases in cardiac output, and cardiac arrest [34, 35, 36].

G. Inotropic therapy

1. In patients with low cardiac output despite adequate fluid resuscitation, dobutamine may be used to increase cardiac output. If used in the presence of low blood pressure, it should be combined with vasopressor therapy.

Grade E.

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. In the absence of measurements of cardiac output, hypotensive patients with severe sepsis may have low, normal or increased cardiac outputs. Therefore, treatment with a combined inotrope/vasopressor such as norepinephrine or dopamine is recommended. When capability exists for monitoring cardiac output in addition to blood pressure, a vasopressor such as norepinephrine and an inotrope such as dobutamine may be used separately to target specific levels of mean arterial pressure and cardiac output.

2. A strategy of increasing cardiac index to achieve an arbitrarily predefined elevated level is not recommended.

Grade A.

Rationale. Two large prospective clinical trials that included critically ill ICU patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal levels by use of dobutamine [37, 38]. The goal of resuscitation should instead be to achieve adequate levels of oxygen delivery ot avoid flow dependant tissue hypoxia.

H. Steroids

1. Intravenous corticosteroids (hydrocortisone 200–300 mg/day, for 7 days in 3 or 4 divided doses or by continuous infusion) are recommended in patients with septic shock who, despite adequate fluid replacement, require vasopressor therapy to maintain adequate blood pressure.

Grade C.

Rationale. One multicenter, randomized, controlled trial (RCT) with patients in severe septic shock showed a significant shock reversal and reduction of mortality in patients with relative adrenal insufficiency (defined as post-ACTH cortisol rise ≤ 9 μg/dl) [39]. Two additional smaller RCTs showed significant effects on shock reversal [40, 41]. In the first study, patients had more severe septic shock (systolic blood pressure [SBP] <90 mmHg despite vasopressors) than in the latter 2 studies (SBP >90 mmHg with vasopressors).

a. Some experts would use a 250 μg ACTH stimulation test to identify responders (>9 μg/dl rise in cortisol 30–60 min post-ACTH administration) and discontinue therapy in these patients. Clinicians should not wait for ACTH stimulation results to administer corticosteroids.

Grade E.

Rationale. One study demonstrated that an incremental increase of >9 μg/dl after 250 μg ACTH stimulation test (responders) identifies survivors of septic shock [42]. A subsequent trial demonstrated that stress dose steroids improved survival in those patients who failed to produce this rise in cortisol with ACTH (non-responders). Treatment with corticosteroids was ineffective in responders

[39]. Recommendations for the identification of relative adrenal insufficiency vary based on different cut-off levels of random cortisol, peak cortisol after stimulation, incremental cortisol increase after stimulation, and combinations of these criteria [43, 44, 45]. In patients with septic shock, clinicians should consider administering a dose of dexamethasone until such time that an ACTH stimulation test can be administered because dexamethasone, unlike hydrocortisone, does not interfere with the cortisol assay.

b. Some experts would decrease dosage of steroids after resolution of septic shock.

Grade E.

Rationale. There has been no comparative study between a fixed duration and clinically guided regimen. Two RCTs used a fixed duration protocol for treatment [39, 41] and in one RCT, therapy was decreased after shock resolution and discontinued after 6 days [40].

c. Some experts would consider tapering the dose of corticosteroids at the end of therapy.

Grade E.

Rationale. One study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids [46].

d. Some experts would add fludrocortisone (50 μg P.O. q.d.) to this regimen.

Grade E.

Rationale. One study added 50 μg fludrocortisone orally [39]. Since hydrocortisone has intrinsic mineralocorticoid activity, there is controversy as to whether fludrocortisone should be added.

2. Doses of corticosteroids higher than >300 mg hydrocortisone daily should not be used in severe sepsis or septic shock for the purpose of treating septic shock.

Grade A.

Rationale. Two randomized prospective clinical trials and 2 meta-analyses concluded that for therapy of severe sepsis or septic shock, high-dose corticosteroid therapy is ineffective or harmful [47, 48, 49, 50]. There may be reasons to maintain higher doses of corticosteroid for medical conditions other than septic shock.

3. In the absence of shock, corticosteroids should not be administered for the treatment of sepsis. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's history of corticosteroid administration or the patient's endocrine history warrants.

Grade E.

Rationale. There are no studies that document that stress doses of steroids improve the outcome of sepsis in the absence of shock unless the patient requires stress dose replacement due to a prior history of steroid therapy or adrenal dysfunction.

I. Recombinant activated protein C (rhAPC)

1. rhAPC is recommended in patients at high risk of death (APACHE II $\geq$25, sepsis-induced multiple organ failure, septic shock, or sepsis-induced ARDS) and no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit of rhAPC (see appendix B for absolute contraindications).

Grade B

Rationale. The inflammatory response in severe sepsis is integrally linked to procoagulant activity and endothelial activation. The inflammatory response in sepsis is procoagulant in the early stages. rhAPC, an endogenous anticoagulant with anti-inflammatory properties, has been shown, in a large, multicenter, randomized, controlled, trial [50], to improve survival in patients with sepsis-induced organ dysfunction.

At present, risk assessment is best determined by bedside clinical evaluation and judgment. Given the uncertainty of risk assessment and the potential for rapid deterioration of patients with severe sepsis and septic shock, once a patient has been identified as at high-risk of death, treatment should begin as soon as possible.

J. Blood product administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as significant coronary artery disease, acute hemorrhage, or lactic acidosis (see recommendations for initial resuscitation), red blood cell transfusion should occur only when hemoglobin decreases to <7.0 g/dl (<70 g/l) to target a hemoglobin of 7.0–9.0 g/dl (70–90 g/l).

Grade B.

Rationale. Although the optimum hemoglobin for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care (TRICC) trial suggest that a hemoglobin of 7–9 g/dl (70–90 g/l) is adequate for most critically ill patients. A transfusion threshold of 7.0 g/dl (70 g/l) was not associated with increased mortality. Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption [51, 52, 53]. This transfusion threshold contrasts with the target of a hematocrit of 30% in patients with low central venous O_2 saturation during the first 6 h of resuscitation of septic shock.

2. Erythropoietin is not recommended as a specific treatment of anemia associated with severe sepsis, but may be used when septic patients have other accepted

reasons for administration of erythropoietin such as renal failure induced compromise of red blood cell production.

Grade B

Rationale. No specific information regarding erythropoietin use in septic patients is available, but clinical trials in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome [54, 55]. Patients with severe sepsis and septic shock may have coexisting conditions that do warrant use of erythropoietin.

3. Routine use of fresh frozen plasma (FFP) to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures is not recommended.

Grade E.

Rationale. Although clinical studies have not assessed the impact of transfusion of FFP on outcomes in critically ill patients, professional organizations have recommended FFP for coagulopathy when there is a documented deficiency of coagulation factors (increased prothrombin time, INR or partial thromboplastin time) and the presence of active bleeding or prior to surgical or invasive procedures [56, 57, 58].

4. Antithrombin administration is not recommended for the treatment of severe sepsis and septic shock.

Grade B.

Rationale. A phase 3 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 [59].

5. In patients with severe sepsis, platelets should be administered when counts are $<5{,}000/mm^3$ (5×10^9/l) regardless of apparent bleeding. Platelet transfusion may be considered when counts are $5{,}000–30{,}000/mm^3$ ($5–30\times10^9$/l) and there is a significant risk of bleeding. Higher platelet counts of $\geq 50{,}000/mm^3$ (50×10^9/l) are typically required for surgery or invasive procedures.

Grade E.

Rationale. Guidelines for transfusion of platelets are derived from consensus opinion and experience in patients undergoing chemotherapy. Recommendations take into account the etiology of thrombocytopenia, platelet dysfunction, risk of bleeding, and presence of concomitant disorders [56, 58].

K. Mechanical ventilation of sepsis-induced acute lung injury (ALI)/acute respiratory distress syndrome (ARDS)

1. High tidal volumes that are coupled with high plateau pressures should be avoided in ALI/ARDS. Clinicians should use as a starting point a reduction in tidal volumes over 1–2 h to a "low" tidal volume (6 ml per kg of lean body weight) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressures less than 30 cmH_2O (See appendix C for formula to calculate predicted body weight).

Grade B.

Rationale. Over the past 10 years several multicenter randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through modulations in tidal volume [60, 61, 62, 63]. These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups [64, 65]. The largest trial of a volume and pressure-limited strategy showed a 9% decrease of all-cause mortality in patients ventilated with tidal volumes of 6 ml/kg of predicted body weight (as opposed to 12 ml/kg) while aiming for a plateau pressure <30 cmH_2O [66].

2. Hypercapnia (allowing p_aCO_2 to increase above normal, so-called permissive hypercapnia) can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes.

Grade C.

Rationale. An acutely elevated p_aCO_2 may have physiologic consequences that include vasodilation, as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small non-randomized series [67, 68]. Patients treated in larger trials that have the goal of limiting tidal volumes and airway pressures have demonstrated improved outcomes, but permissive hypercapnia was not a primary treatment goal in these studies [66]. The use of hypercarbia is limited in patients with pre-existing metabolic acidosis and is contraindicated in patients with increased intracranial pressure. Sodium bicarbonate infusion may be considered in select patients to facilitate use of permissive hypercarbia.

3. A minimum amount of positive end-expiratory pressure (PEEP) should be set to prevent lung collapse at end expiration. Setting PEEP based on severity of oxygenation deficit and guided by the F_IO_2 required to maintain adequate oxygenation is one acceptable approach. (See appendix C for table.) Some experts titrate PEEP according to bedside measurements of thoracopulmonary compliance (to obtain the highest compliance, reflecting lung recruitment).

Grade E.

Rationale. Raising end-expiratory pressure in ALI/ARDS keeps lung units open to participate in gas exchange [69, 70, 71]. This will increase p_aO_2 when PEEP is applied through either an endotracheal tube or a face mask.

4. In facilities with experience, prone positioning should be considered in ARDS patients requiring potentially injurious levels of F_IO_2 or plateau pressure who are not at high risk for adverse consequences of positional changes.

Grade E.

Rationale. Several smaller studies and one larger study have shown that a majority of patients with ALI/ARDS respond to the prone position with improved oxygenation [72, 73, 74, 75, 76]. The large multi-center trial of prone positioning for ≈7 h/day did not show improvement in mortality rates in patients with ALI/ARDS; however, a post hoc analysis suggested improvement in those patients with the most severe hypoxemia by PaO_2/F_IO_2 ratio [75]. Prone positioning may be associated with potentially life-threatening complications, including accidental dislodgement of the endotracheal tube and central venous catheters, but these complications can usually be avoided with proper precautions.

5. Unless contraindicated, mechanically ventilated patients should be maintained semirecumbent, with the head of the bed raised to 45° to prevent the development of ventilator-associated pneumonia.

Grade C.

Rationale. The semi-recumbent position has been demonstrated to decrease the incidence of ventilator-aquired pneumonia [77]. Patients are laid flat for procedures, hemodynamic measurements, and during episodes of hypotension. Consistent return to semi-recumbent position should be viewed as a quality indicator in patients receiving mechanical ventilation.

6. A weaning protocol should be in place and mechanically ventilated patients should undergo a spontaneous breathing trial (SBT) to evaluate ability to discontinue mechanical ventilation when they satisfy the following: (a) arousable, (b) hemodynamically stable (without vasopressor agents), (c) no new potentially serious conditions, (d) low ventilatory and end-expiratory pressure requirements, and (e) requiring levels of F_IO_2 that could be safely delivered with a face mask or nasal cannula. If the SBT is successful, consideration should be given for extubation (Fig. 1). Spontaneous breathing trial options include a low level of pressure support with CPAP 5 cm H_2O or a T-piece.

Grade A.

Rationale. Recent studies demonstrate that daily spontaneous breathing trials reduce the duration of mechanical ventilation [78, 79, 80]. While these studies had limited numbers of patients with documented ALI/ARDS, there is no reason to believe that ALI/ARDS patients would have different outcomes from other critically ill patients. Successful completion of spontaneous breathing trials lead to a high likelihood of successful discontinuation of mechanical ventilation.

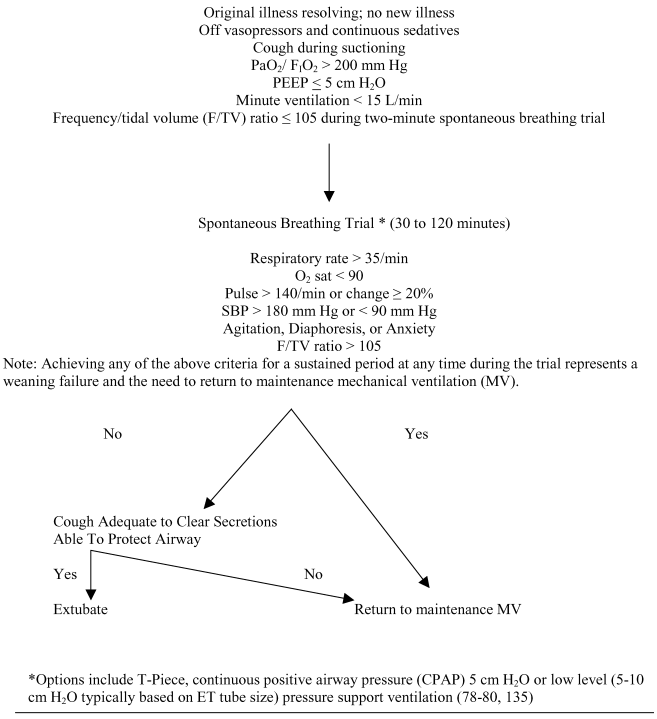

Fig. 1 Use of spontaneous breathing trial in weaning ARDS patients

L. Sedation, analgesia, and neuromuscular blockade in sepsis

1. Protocols should be utilized when sedation of critically ill mechanically ventilated patients is required. The protocol should include the use of a sedation goal, measured by a standardized subjective sedation scale.

Grade B.

2. Either intermittent bolus sedation or continuous infusion sedation to predetermined endpoints (e.g., sedation scales) with daily interruption/lightening of continuous infusion sedation with awakening and retitration, if necessary, are recommended methods for sedation administration.

Grade B.

Rationale. (*L1 and L2*) Mechanically ventilated patients receiving continuous sedation may have a significantly longer duration of mechanical ventilation as well as ICU and hospital length of stay [81]. A daily interruption or

lightening of a "continuous" sedative infusion until the patient is awake may decrease the duration of mechanical ventilation and ICU stay [82]. The use of sedation protocols in mechanically ventilated patients has shown a reduced duration of mechanical ventilation, length of stay, and tracheostomy rates [83].

3. Neuromuscular blockers (NMBs) should be avoided if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBs must be utilized for longer than the first hours of mechanical ventilation, either intermittent bolus as required or continuous infusion with monitoring of depth of block with train of four monitoring should be utilized.

Grade E.

Rationale. Prolonged skeletal muscle weakness has been reported in critically ill patients following the use of intermediate and long-acting NMBs [84, 85, 86, 87, 88, 89, 90, 91]. The risk of prolonged paralysis may be reduced if an intermittent assessment of the depth of neuromuscular blockade is performed [92, 93].

M. Glucose control

1. Following initial stabilization of patients with severe sepsis, maintain blood glucose <150 mg/dl (8.3 mmol/l). Studies supporting the role of glycemic control have used continuous infusion of insulin and glucose. With this protocol, glucose should be monitored frequently after initiation of the protocol (every 30–60 min) and on a regular basis (every 4 h) once the blood glucose concentration has stabilized.

Grade D.

Rationale. A large single-center trial of postoperative surgical patients showed significant improvement in survival when continuous infusion insulin was used to maintain glucose between 80 and 110 mg/dl (4.4–6.1 mmol/l) [94]. Exogenous glucose was begun simultaneously with insulin with frequent monitoring of glucose (every 1 h) and intensity of monitoring greatest at the time of initiation of insulin. Hypoglycemia may occur. There is no reason to think that these data are not generalizable to all severely septic patients. Post hoc data analysis of the trial data revealed that although best results were obtained when glucose was maintained between 80 and 110 mg/dl (4.4 and 6.1 mmol/l), achieving a goal of less than 150 mg/dl (8.3 mmol/l) also improved outcome when compared to higher levels. This goal will likely reduce the risk of hypoglycemia. The control of the blood glucose concentration appears to be more important than the amount of insulin infused [95, 96]. The frequency of blood glucose determinations may require the use of central or arterial catheters for blood sampling.

2. In patients with severe sepsis, a strategy of glycemic control should include a nutrition protocol with the preferential use of the enteral route.

Grade E.

Rationale. When a glycemic control strategy is initiated, hypoglycemia is minimized by providing a continuous supply of glucose substrate. Initially, unless the patient is already profoundly hyperglycemia, this is accomplished with 5% or 10% dextrose infusion and followed by initiation of feeding, preferably by the enteral route, if tolerated [97].

N. Renal replacement

1. In acute renal failure, continuous veno-venous hemofiltration or intermittent hemodialysis are considered equivalent. Continuous hemofiltration offers easier management of fluid balance in hemodynamically unstable septic patients.

Grade B.

Rationale. Studies support the equivalence of continuous and intermittent renal replacement therapies for the treatment of acute renal failure in critically ill patients [98, 99]. Intermittent hemodialysis may be poorly tolerated in the hemodynamically unstable patients. There is no current evidence to support the use of CVVH for the treatment of sepsis independent of renal replacement needs.

O. Bicarbonate therapy

1. Bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements is not recommended for treatment of hypoperfusion-induced lactic acidemia with pH $\geq$7.15. The effect of bicarbonate administration on hemodynamics and vasopressor requirement at lower pH as well as the effect on clinical outcome at any pH has not been studied.

Grade C.

Rationale. There is no evidence to support the use of bicarbonate therapy in the treatment of hypoperfusion-induced acidemia associated with sepsis. Two studies comparing saline and bicarbonate in patients with pH$\geq$7.13–7.15 failed to reveal any difference in hemodynamic parameters or vasopressor requirements between equimolar concentrations of bicarbonate and normal saline with either therapy [100, 101].

P. Deep vein thrombosis prophylaxis

1. Severe sepsis patients should receive DVT prophylaxis with either low-dose unfractionated heparin (UH) or low-molecular weight heparin (LMWH). For septic patients who have a contraindication for heparin use (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage), the use of a mechanical prophylactic device (graduated compression stockings or intermittent compression device) is recommended (unless contraindicated by presence of peripheral vascular disease). In very high-risk patients such as those who have severe sepsis and history of DVT, a combination of pharmacologic and mechanical therapy is recommended.

Grade A.

Rationale. Although no study has been performed specifically in patients with severe sepsis, large trials confirming the benefit of DVT prophylaxis in general ICU populations have included significant numbers of septic patients [102, 103, 104]. This benefit should be applicable to patients with severe sepsis and septic shock.

Q. Stress ulcer prophylaxis

1. Stress ulcer prophylaxis should be given to all patients with severe sepsis. H_2 receptor inhibitors are more efficacious than sucralfate and are the preferred agents. Proton pump inhibitors have not been assessed in a direct comparison with H_2 receptor antagonists and, therefore, their relative efficacy is unknown. They do demonstrate equivalency in ability to increase gastric pH.

Grade A.

Rationale. Although no study has been performed specifically in patients with severe sepsis, large trials confirming the benefit of stress ulcer prophylaxis in general ICU populations have included significant numbers of septic patients [105, 106, 107, 108]. This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the conditions shown to benefit from stress ulcer prophylaxis are frequently present in patients with severe sepsis and septic shock. Stress ulcer prophylaxis is not needed in patients with full enteral nutrition goals established.

R. Consideration for limitation of support

1. Advance care planning, including the communication of likely outcomes and realistic goals of treatment, should be discussed with patients and families. Decisions for less aggressive support or withdrawal of support may be in the patient's best interest.

Grade E.

Rationale. It is too frequent that inadequate physician/family communication characterizes end-of-life care in the ICU. The level of life support given to ICU patients may not be consistent with their wishes. Early and frequent caregiver discussions with patients who face death in the ICU and their loved ones may facilitate appropriate application and withdrawal of life-sustaining therapies.

S. Pediatric considerations

1. Mechanical ventilation. Due to low functional residual capacity (FRC), young infants and neonates with severe sepsis may require early intubation [109]. The principles of lung-protective strategies are applied to children as they are to adults. In premature infants, additional attention is paid to avoiding hyperoxemia to prevent retinopathy.

2. Fluid resuscitation. Intravenous access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in children than in adults. The American Heart Association has developed pediatric advanced life support (PALS) guidelines for emergency establishment of intravascular support [110]. On the basis of a number of studies, it is accepted that aggressive fluid resuscitation with crystalloids or colloids is of fundamental importance to survival of septic shock in children [111, 112]. There is only one randomized, controlled trial comparing the use of colloid to crystalloid resuscitation (dextran, gelatin, lactated Ringers, or saline) in children with dengue shock [111]. All these children survived regardless of the fluid used, but the longest time to recovery from shock occurred in children who received lactated Ringers. Among patients with the narrowest pulse pressure, there was a suggestion that colloids were more effective than crystalloids in restoring normal pulse pressure. Fluid infusion is best initiated with boluses of 20 ml/kg over 5–10 min, titrated to clinical monitors of cardiac output, including heart rate, urine output, capillary refill, and level of consciousness. Children normally have a lower blood pressure than adults and can prevent reduction in blood pressure by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of the adequacy of fluid resuscitation. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 ml/kg but can be much higher [112, 113, 114].

3. Vasopressors/inotropes (should only be used after appropriate volume resuscitation). 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. Depending on which situation exists, inotropic support should be started in the case of fluid refractory shock or a combination of an inotrope together with a vasopressor or a vasodilator. Dopamine is the first choice of support for the pediatric patient with hypotension refractory to fluid resuscitation. The choice of vasoactive agent is determined by the clinical examination. Dopamine-refractory shock may be reversed with epinephrine or norepinephrine infusion [114]. Pediatric patients with low cardiac output states may benefit from use of dobutamine. The use of vasodilators can reverse shock in pediatric patients who remain hemodynamically unstable with a high systemic vascular resistance state, despite fluid resuscitation and implementation of inotropic support [114, 115]. Nitrosovasodilators with a very short half-life (nitroprusside or nitroglycerin) are used as first-line therapy for children with epinephrine-resistant low cardiac output and elevated systemic vascular-resistance shock. Inhaled nitric oxide reduced extracorporeal membrane oxygenation (ECMO) use when given to term neonates with persistant pulmonary artery hypertension of the newborn (PPHN) and sepsis in a randomized controlled trial [116]. When pediatric patients remain in a normotensive low cardiac output and high vascular resistance state, despite epinephrine and nitrosovasodilator therapy, then the use of a phosphodiesterase inhibitor should be strongly considered [117, 118, 119]. Pentoxifylline (not available in the U.S.) improved outcome in premature neonates with sepsis when given for 6 h/day for 5 days in a randomized, controlled trial [120].

4. Therapeutic endpoints. Therapeutic end points are capillary refill of <2 s, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 ml/kg h^{-1}, normal mental status, decreased lactate and increased base deficit and superior vena cava or mixed venous oxygen saturation >70%. When employing measurements to assist in identifying acceptable cardiac output in children with systemic arterial hypoxemia such as cyanotic congenital heart disease or severe pulmonary disease, arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation with oxygen. Optimizing preload optimizes cardiac index (CI). As noted above, blood pressure by itself is not a reliable endpoint for resuscitation. If a pulmonary artery catheter is utilized, therapeutic endpoints are CI >3.3 and <6.0 l/min m^{-2} with normal perfusion pressure (MAP-CVP) for age.

5. Approach. Figure 2 shows a flow diagram summarizing an approach to pediatric septic shock [121].

6. Steroids. Hydrocortisone therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency. Patients at risk include children with severe septic shock and purpura [122, 123], children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. There are no strict definitions, but adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol level below 18 μg/dl (496 nmol/l). There is no clear consensus for the role of steroids or best dose of steroids in children with septic shock. A post 30 min or 60 min ACTH stimulation test rise in cortisol of $\leq$9 μg/dl (248 nmol/l) also makes that diagnosis. There are 2 randomized controlled trials that used "shock dose" hydrocortisone (25 times higher than the stress dose) in children, both in dengue fever. The results were conflicting [124, 125]. Dose recommendations vary from 1–2 mg/kg for stress coverage (based on clinical diagnosis of adrenal insufficiency) to 50 mg/kg for empiric therapy of shock followed by the same dose as a 24 h infusion.

7. Protein C and activated protein C. Protein C levels in children reach adult values at the age of 3 years. This might indicate that the importance of protein C supplementation either as protein C concentrate or as rhAPC is even greater in young children than in adults. There has been one dose finding, placebo-controlled study performed using protein C concentrate. This study was not powered to show an effect on mortality, but did show a positive effect on sepsis-induced coagulation disturbances [126, 127]. No randomized studies using rhAPC have been performed.

8. Granulocyte macrophage colony stimulating factor (GM-CSF). Growth factors or white blood cell transfusions are given to patients with neutropenic sepsis secondary to chemotherapy or white blood cell primary immune deficiency. A randomized, controlled trial showed improved outcomes in neonates with sepsis and an absolute neutrophil count <1,500/μl (1.5×10^9/l) treated with a 7-day course of GM-CSF [128, 129].

9. DVT prophylaxis. Most DVTs in young children are associated with central venous lines (CVLs). Femoral venous lines are commonly used in children, and CVL-associated DVT occurs in approximately 25% of children with a femoral CVL. There are no data on use of heparin prophylaxis to prevent DVT in children.

10. Stress ulcer prophylaxis. No studies have been performed in children analyzing the effect of stress ulcer prophylaxis. Studies have shown that the rate of clinically important gastrointestinal (GI) bleeding in children occurs at rates similar to adults [130, 131]. As in adults, coagulopathy and mechanical ventilation are risk factors for clinically important GI bleeding. Stress ulcer prophylaxis

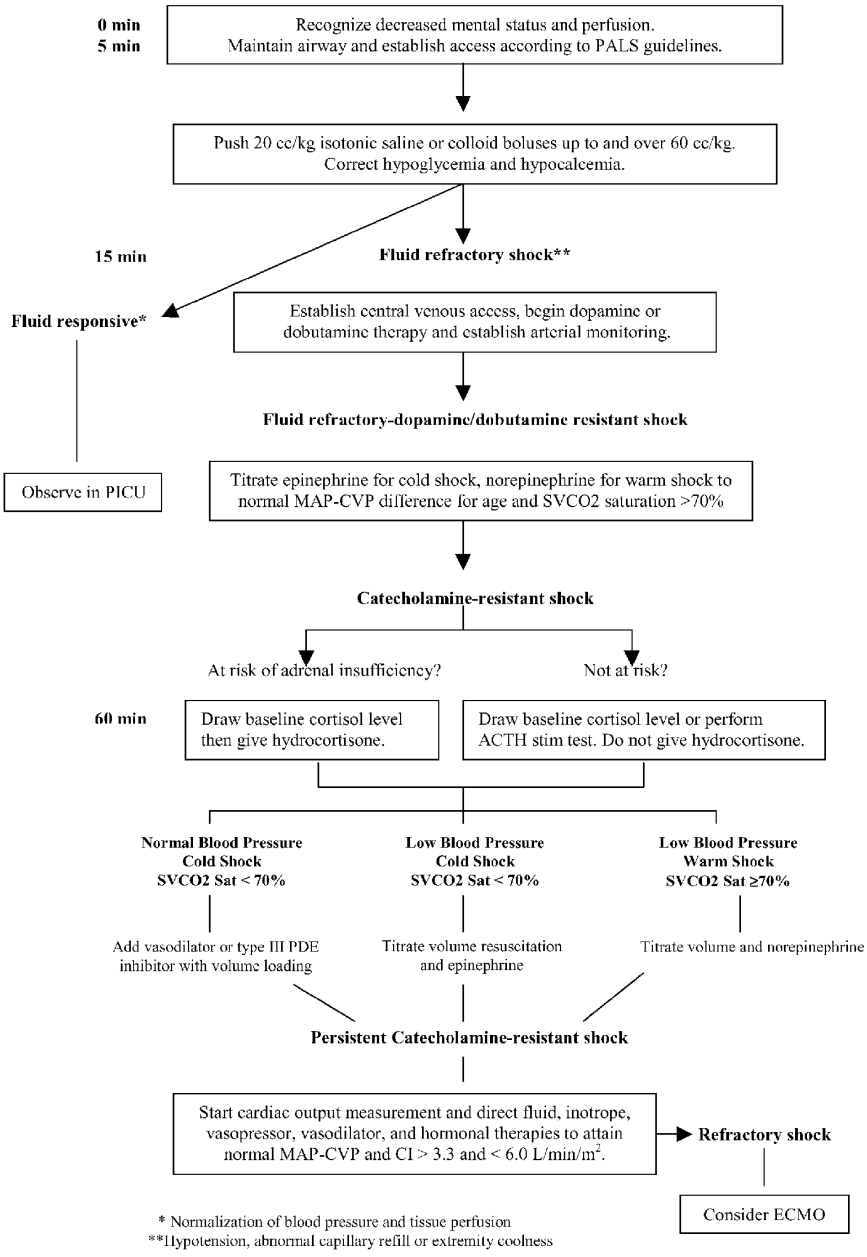

Fig. 2 Flow diagram summarizing an approach to pediatric septic shock

strategy is commonly used in mechanically ventilated children, usually with H_2 blockers. Its effect is not known.

11. Renal replacement therapy. Continuous venovenous hemofiltration (CVVH) may be clinically useful in children with anuria/severe oliguria and fluid overload, but no large RCTs have been performed.

12. Glycemic control. 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/kg min^{-1} or maintenance fluid intake with glucose 10%in NaCl 0.45% is advised. There are no studies in pediatric patients analyzing the effect of rigid glycemic control using insulin. This should only be done with frequent glucose monitoring in view of the risks for hypoglycemia.

13. Sedation/analgesia. Appropriate sedation and analgesia for children who are mechanically ventilated is the standard of care, although there are no data supporting any particular drugs or drug regimens.

14. Blood products. In the absence of data, it is reasonable to maintain hemoglobin concentration within the normal

range for age in children with severe sepsis and septic shock at $\geq$10 g/dl (100 g/l).

15. Intravenous immunoglobulin (IVIG). Polyclonal IVIG has been reported to reduce mortality and is a promising adjuvant in the treatment of sepsis and septic shock. In children, however, all the trials have been small, and the totality of the evidence is insufficient to support a robust conclusion of benefit. Adjunctive therapy with monoclonal IVIGs remains experimental [132].

16. Extracorporeal membrane oxygenation (ECMO). ECMO has been used in septic shock in children, but its impact is not clear. Survival from refractory shock or respiratory failure associated with sepsis is 80% in neonates and 50% in children. There is one study analyzing 12 patients with meningococcal sepsis on ECMO; 8 of the 12 patients survived, with 6 leading functionally normal lives at a median of 1 year (range, 4 months to 4 years) of follow-up. Children with sepsis on ECMO do not perform worse than children without sepsis at long-term follow-up [133, 134].

Summary and future directions

Although evidence-based recommendations have been frequently published in the medical literature, documentation of impact on patient outcome is limited. The next phase of the Surviving Sepsis Campaign is targeted to implement a core set of the above recommendations in hospital environments where change in behavior and clinical impact can be measured. The first step in this next phase will be a joint effort with the Institute of Healthcare Improvement (IHI) to deploy a "change bundle" based on a core set of the above recommendations into the IHI collaborative system. Chart review will identify and track change in practice and clinical outcome. Engendering evidence-based change through motivational strategies while monitoring and sharing impact with health care practitioners is the key to improving outcome in severe sepsis.

The reader is reminded that although this document is static, the optimum treatment of severe sepsis and septic shock is a dynamic and evolving process. New interventions will be proven and established interventions, as stated in the current recommendations, may need modification. This publication represents the start of what will be an ongoing process. The Surviving Sepsis Campaign and the consensus committee members are committed to creating a dynamic, electronic, Web-based guideline process. We foresee that as new evidence becomes available, revisions will be channeled through the committee and, following sponsoring organization approval, changes will be noted on the electronic guidelines, which are available for posting on all sponsoring organization Web sites. We anticipate a formal updating process annually.

Acknowledgment *Founding of the Surviving Sepsis Campaign.* The ESICM, SCCM and International Sepsis Forum have established the Surviving Sepsis Campaign with the aim of improving the care of septic patients. The first phase of the Campaign was built around the Barcelona ESICM congress and included the initial Barcelona Declaration, a media campaign that identified sepsis as a killer and the need to make progress in public awareness and to reduce mortality, and two surveys performed among physicians. The cost of phase I was approximately EUR 553,227, and was supported by unrestricted educational grants from Eli Lilly (94%), Edwards (3%) and Baxter (3%). Producing the present guidelines document was the phase II of the Campaign. For this process, the sponsor companies have been entirely separated from the process by which the guidelines were developed by the many contributors, whose conflicts of interest have been collected in accordance with SCCM guidance (see document). The costs for this phase included mainly the costs of the meeting, teleconference and website update, amounted to approximately EUR 125,006, and were beared by unrestricted educational grants from Eli Lilly (90%) and Edwards (10%). Most of the expense for this effort has been time by the committee who received no reimbursement.

Appendix

Appendix A

The following Table shows the source control procedure

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

Appendix B

This Table shows the contraindications for use of rhAPC

Contraindications to use of rhAPC
(See labeling instructions for relative contraindications[a])
rhAPC increases the risk of bleeding. rhAPC is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity
Active internal bleeding
Recent (within 3 months) hemorrhagic stroke
Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
Trauma with an increased risk of life-threatening bleeding
Presence of an epidural catheter
Intracranial neoplasm or mass lesion or evidence of cerebral herniation

[a] The committee recommends that platelet count be maintained at 30,000 or greater during infusion of rhAPC.
Physicians' Desk Reference. 57th edn. Montvale, NJ, Thompson PDR, 2003, pp 1875–1876.
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Appendix C

This Table shows the conditions for ARDSNET ventilation management [66]

ARDSNET ventilator management
Assist control mode—volume ventilation
Reduce tidal volume to 6 ml/kg predicted 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%
The chart below gives anticipated PEEP setting at various F_IO_2 requirements:

F_IO_2	.3	.4	.4	.5	.5	.6	.7	.7	.7	.8	.9	.9	.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 blood saturation; PEEP, positive end-expiratory pressure

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