Crit Care & Shock (2004) 7: 171- 194

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

R. Phillip Dellinger, Jean M. Carlet, Henry Masur, Herwig Gerlach, Thierry Calandra, Jonathan Cohen, Juan Gea-Banacloche, Didier Keh, John C. Marshall, Margaret M. Parker, Graham Ramsay, Janice L. Zimmerman, Jean-Louis Vincent, Mitchell M. Levy, for the Surviving Sepsis Campaign Management Guidelines Committee

Abstract

***Objective*: In 2003, critical care and infectious disease experts representing 11 international organizations developed 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.**

***Methods*: We used a modified Delphi methodology for grading recommendations, built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations were provided to contrast adult and pediatric management.**

***Results*: Key recommendations, listed by category and not by hierarchy, include early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition; appropriate diagnostic studies to ascertain causative organisms before starting antibiotics; early administration of broad-spectrum antibiotic therapy; reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate; a usual 7˘10 days of antibiotic therapy guided by clinical response; source control with attention to the method that balances risks and benefits; equivalence of crystalloid and colloid resuscitation; aggressive fluid challenge to restore mean circulating filling pressure; vasopressor preference for norepinephrine and dopamine; cautious use of vasopressin pending further studies; avoiding low-dose dopamine administration for renal protection; consideration of dobutamine inotropic therapy in some clinical situations; avoidance of supranormal oxygen delivery as a goal of therapy; stress-dose steroid therapy for septic shock; use of recombinant activated protein C in patients with severe sepsis and high risk for death; with resolution of tissue hypoperfusion and in the absence of coronary artery disease or acute hemorrhage, targeting a hemoglobin of 7˘9 g/dL; appropriate use of fresh frozen plasma and platelets; a low tidal volume and limitation of inspiratory plateau pressure strategy for acute lung injury and acute respiratory distress syndrome; application of a minimal amount of positive end-expiratory pressure in acute lung injury/acute respiratory distress syndrome; a semirecumbent bed position unless contraindicated; protocols for weaning and sedation/analgesia, using either intermittent bolus sedation or continuous infusion sedation with daily interruptions/lightening; avoidance of neuromuscular blockers, if at all possible; maintenance of blood glucose <150 mg/dL after initial stabilization; equivalence of continuous veno-veno hemofiltration and intermittent hemodialysis; lack of utility of bicarbonate use for pH >7.15; use of deep vein thrombosis/stress ulcer prophylaxis; and consideration of limitation of support where appropriate. Pediatric considerations included a more likely need for intubation due to low functional residual capacity; more difficult intravenous access; fluid resuscitation based on weight with 40˘60 mL/kg or higher needed; decreased cardiac output and increased systemic vascular resistance as the most common hemodynamic profile; greater use of physical examination therapeutic end points; unsettled issue of high-dose steroids for therapy of septic shock; and greater risk of hypoglycemia with aggressive glucose control.**

***Conclusion*: Evidence-based recommendations can be made regarding many aspects of the acute management of sepsis and septic shock that are hoped to 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 as some important new knowledge becomes available. (Crit Care Med 2004; 32:858 ˘873)**

Keywords: sepsis; severe sepsis; septic shock; sepsis syndrome; infection; guidelines; evidence-based medicine; Surviving Sepsis Campaign

Surviving Sepsis Campaign Management Guidelines Committee. Chairs: R. Phillip Dellinger, MD*; Henry Masur, MD; Jean M. Carlet, MD; Herwig Gerlach, MD, PhD**. Committee Members: Richard J. Beale,
MD**; Marc Bonten, MD; Christian Brun-Buisson, MD; Thierry Calandra, MD; Joseph A. Carcillo, MD; Jonathan Cohen, MD**; Catherine Cordonnier, MD; E. Patchen Dellinger, MD; Jean-Francois Dhainaut, MD, PhD; Roger G. Finch, MD; Simon Finfer, MD; Francois
A. Fourrier, MD; Juan Gea-Banacloche, MD; Maurene A. Harvey, RN, MPH**; Jan A. Hazelzet, MD; Steven M. Hollenberg, MD; James H. Jorgensen, PhD; Didier Keh, MD; Mitchell M. Levy, MD*; Ronald V. Maier, MD; Dennis G. Maki, MD; John J. Marini, MD; John C. Marshall, MD; Steven M. Opal, MD; Tiffany M. Osborn, MD; Margaret M. Parker, MD**; Joseph E. Parrillo, MD; Graham Ramsay, MD*; Andrew Rhodes, MD; Jonathan E. Sevransky, MD; Charles L. Sprung, MD, JD**; Antoni Torres, MD; Jeffery S. Vender, MD; Jean-Louis Vincent, MD, PhD**; Janice L. Zimmerman, MD. Associate Members: E. David Bennett, MD; Pierre-Yves Bochud, MD; Alain Cariou, MD; Glenn S. Murphy, MD; Martin Nitsun, MD; Joseph W. Szokol, MD; Stephen Trzeciak, MD; Christophe Vinsonneau, MD. *Executive Committee, Surviving Sepsis Campaign. **Steering Committee, Surviving Sepsis Campaign. The Surviving Sepsis Campaign is administered jointly by the European Society of Intensive Care Medicine, International Sepsis Forum, and the Society of Critical Care Medicine and is supported in part by unrestricted educational grants from Baxter Bioscience, Edwards Lifesciences, and Eli Lilly and Company (majority sponsor). Use of trade names or names of commercial sources is for information only and does not imply endorsement by the Society of Critical Care Medicine. The authors and the publisher have exercised great care to ensure that drug dosages, formulas, and other information presented in this publication are accurate and in accord with the professional standards in effect at the time of publication. Readers are, however, advised to always check the manufacturer's product information sheet that is packaged with the respective products to be fully informed of changes in recommended dosages, contraindications, and the like before prescribing or administering any drug. Also published in *Intensive Care Medicine* (May).

Address requests for reprints to:
R. Phillip Dellinger,MD, Cooper Health Systems, One Cooper Plaza,
393 Dorrance, Camden, NJ 08103.

Sponsoring Organizations: American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

The mortality rate 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 likely 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, an international effort to increase awareness and improve outcome in severe sepsis. Meeting expenses as well as staff support for guidelines creation were provided by unrestricted industry educational grants as listed. There were no industry members of the committee. There was no industry input into guidelines development and no industry presence at any of the meetings. Industry awareness or comment on the recommendations was not allowed. The sponsors of the educational grants did not see the recommendations until the manuscript was peer reviewed and accepted for publication in final form. Phase I of the Surviving Sepsis Campaign was initiated in October 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**, adapted from Ref. 3). The methods for this document build on a 2001 publication sponsored by the International Sepsis Forum and use the same method of grading recommendations (4). The supplement submission will include background material, questions posed that led to the recommendation, and expanded rationale. This executive summary is targeted to be concise and user friendly for the bedside clinician. The 2001 pub-

Table 1. Grading system

Grading of recommendations

A. Supported by at least two level I investigations
B. Supported by one level I investigation
C. Supported by level II investigations only
D. Supported by at least one level III investigation
E. Supported by level IV or V evidence

Grading of evidence

I. Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error of 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. Nonrandomized, contemporaneous controls
IV. Nonrandomized, historical controls and expert opinion
V. Case series, uncontrolled studies, and expert opinion

lication that was used as a starting point for the current process included a MEDLINE search for clinical trials in the preceding 10 yrs, supplemented by a manual search of other relevant journals. Subtopics for each recommendation were crossreferenced to sepsis, severe sepsis, septic shock, sepsis syndrome, and infection. The Surviving Sepsis Campaign guidelines considered the evidence in the 2001 publication (through 1999) and repeated the process for 2000 through 2003. The committee process began in June 2003 with a meeting featuring the first presentations of data and recommendations. 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 two or three 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 evidence existed for outcome benefit in critically ill populations known to contain a larger number of sepsis patients, these trials were considered in determination of recommendation grading. A strict evidence-based methodology with a scoring system was not used. The goal was total consensus, which was reached in all recommendations except two. In those circumstances (recommendations C3 and H1), the solution was achieved with the inclusion of subrecommendations that expressed some difference 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, and individuals were not assigned to a subgroup topic if they had a potential conflict of interest. A full listing of all potential conflicts of interest is included with this article. Following that meeting, the process continued with further refinement of recommendations through electronic communication among committee members. A second meeting of core members of the committee occurred in early October 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 variable such as survival or length of ICU stay. A grade of A, B, or C required randomized trials. Recommendations are graded and followed with 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 concentration identifies tissue hypoperfusion in patients at risk who are not hypotensive. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol: Central venous pressure: 8˘12 mm Hg Mean arterial pressure ≥65 mm Hg Urine

output ≥0.5 mL—kg^{-1}—hr^{-1} Central venous (superior vena cava) or mixed venous oxygen saturation ≥70%

Grade B

Rationale. Early goal-directed therapy 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 previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged central venous and mixed venous oxygen saturation to be equivalent. Either intermittent or continuous measurements of oxygen 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 central venous pressure of 12˘15 mm Hg is recommended to account for the increased intrathoracic pressure. Similar consideration may be warranted 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 of improving intravascular filling.

2. During the first 6 hrs of resuscitation of severe sepsis or septic shock, if central venous oxygen saturation or mixed venous oxygen saturation of 70% is not achieved with fluid resuscitation to a central venous pressure of 8˘12 mm Hg, then transfuse packed red blood cells to achieve a hematocrit of ≥30% and/or administer a dobutamine infusion (up to a maximum of 20 μg—kg^{-1}—min^{-1}) to achieve this goal.

Grade B

Rationale. The protocol used in the study cited previously targeted an increase in mixed venous oxygen saturation to ≥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. To optimize identification of causative organisms, at least two blood cultures should be obtained with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (≥48 hrs) inserted. Cultures of other sites 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., >2 hrs 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 to maximize the likelihood of a satisfactory response to therapy. However, even in the most organized and well-staffed healthcare facilities, transport of patients can be dangerous, as can placing patients in outside-unit imaging devices that are difficult to access and monitor.

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 premixed 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 empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that 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 empirical 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 healthcare facility.

The initial selection of an empirical antimicrobial regimen should be broad enough, according to these 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˘12).

Although restricting the use of antibiotics, and particularly broad-spectrum antibiotics, is important for limiting superinfection and for decreasing the development of antibioticresistant 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 ensure that serum concentrations are attained that maximize ef-ficacy and minimize toxicity, (13˘16).

3. The antimicrobial regimen should always be reassessed after 48˘72 hrs on the basis of microbiological and clinical data with the aim of using a narrowspectrum 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˘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 noninfectious 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 on infection amenable to source control measures, specifically the drainage of an abscess or local focus on infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination (17). (See Appendix A for examples of potential sites needing source control.)

Grade E

Rationale. Healthcare 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, fistulas, or inadvertent organ injury; in general, the intervention that accomplishes the source control objective with the least physiologic upset should be employed, for example, 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 bloodstream 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˘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 mins 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 develop-

ment of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hrs of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period.

F. Vasopressors

1. 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 catheter as soon as available) is the first-choice vasopressor agent to correct hypotension in septic shock.

Grade D

Rationale. Although there is no highquality 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 with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic (25, 27˜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 with these catheters also allows beatto- beat analysis so that decisions regarding therapy can be based on immediate blood pressure information (25). Placement of an arterial catheter in the emergency department is typically not possible or practical. It is important to appreciate the complications of arterial catheter 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 highdose 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 units/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 <2 or 2.5 L—min-1-m-2, and it should be used with caution in patients with cardiac dysfunction. Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock, concentrations decrease to normal range in the majority of patients between 24 and 48 hrs (33). This has been called relative vasopressin defi-ciency*f* since in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. Doses of vasopressin >0.04 units/min have been associated with myocardial ischemia, significant decreases in cardiac output, and cardiac arrest (34˘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 the 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 or avoid flow-dependent tissue hypoxia.

H. Steroids

1. Intravenous corticosteroids (hydrocortisone 200˘300 mg/day, for 7 days in three or four 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 multiple-center, randomized, controlled trial (RCT) with patients in severe septic shock showed a significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as post-adrenocorticotropic hormone [ACTH] cortisol increase ≤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 <90 mm Hg despite vasopressors) than in the latter two studies (systolic blood >90 mm Hg with vasopressors).

a. Some experts would use a 250-µg ACTH stimulation test to identify responders (>9 µg/dL increase in cortisol 30˘60 mins 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 increase in cortisol with ACTH (nonresponders). Treatment with corticosteroids was ineffective in responders (39).

Recommendations for the identification of relative adrenal insufficiency vary based on different cutoff levels of random cortisol, peak cortisol after stimulation, incremental cortisol increase after stimulation, and combinations of these criteria (43˘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 inone 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 orally four times per day) to this regimen.

Grade E

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

2. Doses of corticosteroids >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 two meta-analyses concluded that for therapy of severe sepsis or septic shock, high-dose corticosteroid therapy is ineffective or harmful (47˘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 documenting 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 Human Activated Protein C (rhAPC)

1. rhAPC is recommended in patients at high risk of death (Acute Physiology and Chronic Health Evaluation II ≥25, sepsis-induced multiple organ failure, septic shock, or sepsis-induced acute respiratory distress syndrome [ARDS]) and with no absolute contraindication related to bleeding risk or relative contraindication that outweighs the potential benefit of rhAPC (see Appendix B for absolute contraindications and prescription information for warnings).

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, multiplecenter, randomized, controlled trial (50), to improve survival in patients with sepsisinduced 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.

Grade B

Rationale. Although the optimum hemoglobin for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin of 7˜9 g/dL (70˜90 g/L) is adequate for most critically ill patients. A transfusion threshold of 7.0 g/dL (70 g/L) was not associated with increased mortality rate. Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption (51˜53). This transfusion threshold contrasts with the target of a hematocrit of 30% in patients with low central venous oxygen saturation during the first 6 hrs 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 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 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 (56˜58).

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

Grade B

Rationale. A phase III clinical trial of highdose 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 <5000/mm3 (5 x 10^9/L) regardless of apparent bleeding. Platelet transfusion may be considered when counts are 5000˜30,000/mm^3 (5˜30 x 10^9/L) and there is a significant risk of bleeding. Higher platelet counts (≥50,000/mm^3 [50 x 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)/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 hrs to a low*f* tidal volume (6 mL per kilogram of predicted body weight) as a goal in conjunction with the goal of maintaining endinspiratory plateau pressures <30 cm H_2O. (See Appendix C for a formula to calculate predicted body weight.)

Grade B

Rationale. Over the past 10 yrs, several multiple-center randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through modulations in tidal volume (60˜63). These studies showed dif-

fering 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 cm H_2O (66).

2. Hypercapnia (allowing $Paco_2$ 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 $Paco_2$ may have physiologic consequences that include vasodilation as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small nonrandomized series (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 preexisting 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 endexpiratory pressure should be set to prevent lung collapse at end-expiration. Setting positive end-expiratory pressure based on severity of oxygenation deficit and guided by the FIO_2 required to maintain adequate oxygenation is one acceptable approach. (See Appendix C.) Some experts titrate positive end-expiratory pressure 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˘71). This will increase PaO2 when positive end-expiratory pressure 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 FIO_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˘76). The large multiple-center trial of prone positioning for ≈7 hrs/day did not show improvement in mortality rates in patients with ALI/ARDS; however, a *post hoc* analysis suggested improvement in those patients with the most severe hypoxemia by PaO_2/FIO_2 ratio (75). Prone positioning may be associated with potentially life-threatening complications, including accidental dislodgment of the endotracheal tube and central venous catheters, but these complications can usually be avoided with proper precautions.

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 semirecumbent position has been demonstrated to decrease the incidence of ventilator-required pneumonia (77). Patients are laid flat for procedures, hemodynamic measurements, and during episodes of hypotension. Consistent return to semirecumbent 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 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) requiring levels of FIO_2 that could be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (see Appendix D). Spontaneous breathing trial options include a low level of pressure support with continuous positive airway pressure 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 ˘ 80). Although these studies had lim-

ited 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 leads to a high likelihood of successful discontinuation of mechanical ventilation.

L. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. Protocols should be used 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 end points (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*f* 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 should be avoided if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If neuromuscular blockers must be used 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 used.

Grade E

Rationale. Prolonged skeletal muscle weakness has been reported in critically ill patients following the use of intermediate- and long-acting neuromuscular blockers (84˜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 mins) and on a regular basis (every 4 hrs) 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 hr) 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 <150 mg/dL (8.3 mmol/L) also improved outcome when compared with higher concentrations. 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, and in the absence of hemodynamic instability, continuous venovenous hemofiltration and 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 hemodynamically unstable patients. There is no current evidence to support the use of continuous venovenous hemofiltration 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 hypoperfusioninduced lactic acidemia with pH ≥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 ≥7.13˘7.15 failed to reveal any difference in hemodynamic variables 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 deep vein thrombosis (DVT) prophylaxis with either low-dose unfractionated heparin or low-molecular weight heparin. 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 the 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˘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.

Recommendation: 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˘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 (coagulopathy, mechanical ventilation, hypotension) are frequently present in patients with severe sepsis and septic shock.

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, young infants and neonates with severe sepsis may require early intubation (109). The principles of lungprotective 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 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 Ringer s solution, 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 Ringer s solution. 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 mins, 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 end point for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of 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˘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. Dopaminerefractory shock may reverse 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 persistent pulmonary artery hypertension of the newborn 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˘119). Pentoxifylline (not available in the United States) improved outcome in premature neonates with sepsis when given for 6 hrs/day for 5 days in a randomized, controlled trial (120).

4. *Therapeutic End Points.* Therapeutic end points are capillary refill of <2 secs, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL—kg^{-1}—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 ac-

ceptable 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. As noted previously, blood pressure by itself is not a reliable end point for resuscitation. If a pulmonary artery catheter is used, therapeutic end points are cardiac index >3.3 and <6.0 L—m**i**n^{-1}—m^{-2} with normal perfusion pressure (mean arterial pressure/central venous pressure) for age.

5. *Approach to Pediatric Septic Shock.* **Figure 1** 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 concentration <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- or 60-min ACTH stimulation test increase in cortisol of <9 μg/dL (248 nmol/L) also makes that diagnosis. Two randomized controlled trials used shock dose*f* 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 empirical therapy of shock followed by the same dose as a 24-hr infusion.

7. *Protein C and Activated Protein C.* Protein C concentrations in children reach adult values at the age of 3 yrs. This might indicate that the importance of protein C supplementation either as protein C con centrate 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 rate 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.* 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 <1500/μL (1.5 ˘ 10^9/L) treated with a 7-day course of granulocyte macrophage colony stimulating factor (128, 129).

9. *DVT Prophylaxis.* Most DVTs in young children are associated with central venous catheters. Femoral venous catheters are commonly used in children, and central venous catheter-associated DVT occurs in approximately 25% of children with a femoral central venous catheter. 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 bleeding in children occurs at rates similar to adults (130, 131). As in adults, coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding. Stress ulcer prophylaxis strategy is commonly used in mechanically ventilated children, usually with H2 blockers. Its effect is not known.

11. *Renal Replacement Therapy.* Continuous venovenous hemofiltration 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 m**g**—k**g**$^{-1}$—m**i**n^{-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 venti-

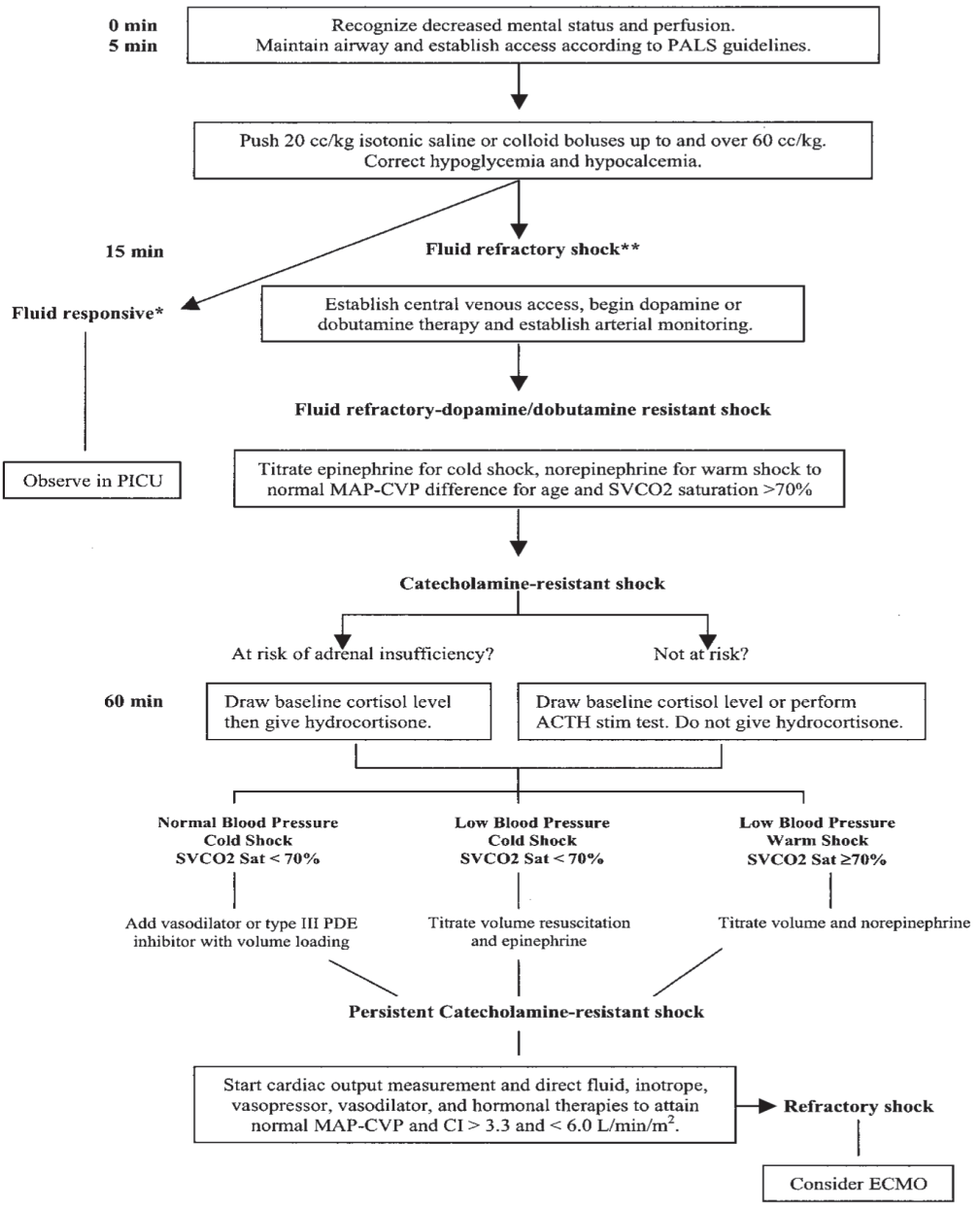


Figure 1. Resuscitation of pediatric septic shock. Adapted from Ref. 121. *Normalization of blood pressure and tissue perfusion; **hypotension, abnormal capillary refill, or extremity coolness.

lated are 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 (≥10 g/dL [100 g/L]).

15. *Intravenous Immunoglobulin.* Polyclonal intravenous immunoglobulin has been reported to reduce mortality rate 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 intra-

venous immunoglobulins remains experimental (132).

16. *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; eight of the 12 patients survived, with six leading functionally normal lives at a median of 1 yr (range, 4 months to 4 yrs) of follow-up. Children with sepsis on ECMO do not perform worse than children without sepsis at long-term follow-up (133˘135).

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 previous 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 to deploy a change bundle*f* based on a core set of the previous recommendations into the Institute of Healthcare Improvement 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 healthcare 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

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 meeting in 2002 and included the initial Barcelona Declaration, a medical 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 $702,598, and was supported by unrestricted educational grants from Eli Lilly (94%), Edwards (3%), and Baxter (3%). Producing the present guidelines document was phase II of the Campaign. For this, 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 below). The costs for this phase mainly included the meeting, teleconferences, and website update and amounted to approximately $158,758, and were borne 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.

Faculty Disclosures—Potential Conflicts of Interest

Speakers bureau, consultant fees, or research grants; Richard J. Beale, MD (Eli Lilly, Fresenius Hemocare and Fresenius Kabi); E. David Bennett, MD (Deltex, Ltd.); Pierre-Yves Bochud, MD (Swiss National Science Foundation); Christian Brun-Buisson, MD (Arrow Int l, Eli Lilly, Glaxo-Smith-Kline, Roche, Wyeth-Lederle); Thierry Calandra, MD (Pfizer, Merck, NatImmune); Jean M. Carlet, MD (Eli Lilly, Anbics, Novo Nordisk, Wyeth Lederle, Fujisawa, Glaxo-Smith-Kline, Bayer, Abbott, Intrabiotics); Jonathan Cohen, MD (Glaxo-Smith-Kline); Catherine Cordonnier, MD (Gilead Science, Merck, Pfizer, Fujisawa); E. Patchen Dellinger, MD (Glaxo-Smith-Kline, Bayer, Eli Lilly, Merck, Wyeth-Ayerst, Pfizer, Ortho-McNeil, Chiron, Versicor, InterMune, Peninsula); R. Phillip Dellinger, MD (Aventis, Bayer, Cubist, Edwards, Eli Lilly, Ortho Biotech, Wyeth-Ayerst); Roger G. Finch, MD (Cubist, Bayer, Glaxo-Smith-Kline, AstraZeneca, Bristol Myers Squibb, Aventis); Francois A. Fourrier, MD (Laboratoire Francais du fractionnement et des biotechnologies [LFB]); Jan A. Hazelzet, MD (Baxter, Eli Lilly); James H. Jorgensen, PhD (bio- Merieux Inc., Becton-Dickinson); Didier Keh, MD (Deutsche Forschungsgemeinschaft [DFG]); Mitchell M. Levy, MD (Eli Lilly, Edwards Lifesciences, OrthoBiotech); Dennis G. Maki, MD (Eli Lilly, Becton Dickinson, Johnson and Johnson); John C. Marshall, MD (Glaxo-Smith-Kline, Eli Lilly, Wyeth-Ayerst, Eisai, Centocor, Boehringer-Ingelheim); Henry Masur, MD (Cubist); Glenn S. Murphy, MD (Organon, Inc.); Steven M. Opal, MD (Genetics Institute, Chiron, Eli Lilly); Margaret M. Parker, MD (Johnson & Johnson [Ortho Biotech] ˘ mem-

ber of Independent Data Monitoring Committee for epo trial); Joseph E. Parrillo, MD (Eisai American, Inc., Schering-Plough Co., Glaxo-Smith-Kline, Medinox, Inc., Chiron Corp., Edwards Lifesciences, Ortho Biotech); Andrew Rhodes, MD (Edwards Lifesciences); Charles L. Sprung, MD, JD (AstraZeneca, European Commission, Eli Lilly); Antoni Torres, MD (Aventis, Abbott, Bayer); Stephen Trzeciak, MD (Aventis, Eli Lilly, Edwards Lifesciences); Jeffery S. Vender, MD (Abbott Pharmaceuticals); Jean-Louis Vincent, MD, PhD (Baxter, Brahms, BMS, Eli Lilly, Glaxo-Smith-Kline, Edwards, Pfizer); Janice L. Zimmerman, MD (Glaxo-Smith-Kline, Cubist). Direct financial interest ˘ stock ($10,000 or more) or partial ownership; None. Faculty with no relationship to disclose; Marc Bonten, MD; Joseph A. Carcillo, MD; Alain Cariou, MD; Jean-Francois Dhainaut, MD, PhD; Simon Finfer, MD; Juan Gea-Banacloche, MD; Herwig Gerlach, MD, PhD; Maurene A. Harvey, RN, MPH; Steven M. Hollenberg, MD; Ronald V. Maier, MD; John J. Marini, MD; Martin Nitsun, MD; Graham Ramsay, MD; Jonathan E. Sevransky, MD; Joseph W. Szokol, MD; Christophe Vinsonneau, MD.

Printed with the permission of The Society of Critical Care Medicine, The European Society of Intensive Care Medicine, and the International Sepsis Forum. Dellinger RP, Carlet JM, Masur H, et al: **Surviving Sepsis Campaign Guidelines for management of severe sepsis and septic shock**. Crit Care Med 2004 March; 32(3):858-873.

References

1. Dellinger RP: Cardiovascular management of septic shock. *Crit Care Med* 2003; 31:946˘955
2. Friedman G, Silva E, Vincent JL: Has the mortality of septic shock changed with time? *Crit Care Med* 1998; 26:2078˘2086
3. Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989; 95:2S˘4S
4. Sprung CL, Bernard GR, Dellinger RP: Introduction. *Intensive Care Med* 2001; 27(Suppl):S1˘S2
5. 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
6. 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
7. 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
8. Mermel LA, Maki DG: Detection of bacteremia in adults: Consequences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270˘272
9. McCabe WR, Jackson GG: Gram negative bacteremia. *Arch Intern Med* 1962; 110:92˘100
10. Kreger BE, Craven DE, McCabe WR: Gram negative bacteremia. IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 1980; 68:344˘355
11. 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
12. 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
13. Hatala R, Dinh T, Cook DJ: Once-daily aminoglycoside dosing in immunocompetent adults: A meta-analysis. *Ann Intern Med* 1996; 124:717˘725
14. 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
15. Amsden GW, Ballow CH, Bertino JS: Pharmacokinetics and Pharmacodynamcis of Anti-infective Agents. *In:* Principles and Practice of Infectious Diseases. Fifth Edition. Mandell GL, Bennett JE, Dolin R (Eds). Philadelphia, Churchill Livingstone, 2000, pp 253˘261
16. Hyatt JM, McKinnon PS, Zimmer GS, et al: The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcomes. Focus on antibacterial agents. *Clin Pharmacokinet* 1995; 28:143˘160
17. Jimenez MF, Marshall JC: Source control in the management of sepsis. *Intensive Care Med* 2001; 27:S49˘S62
18. Bufalari A, Giustozzi G, Moggi L: Postoperative intraabdominal abscesses: Percutaneous versus surgical treatment. *Acta Chir Belg* 1996; 96:197˘200
19. Moss RL, Musemeche CA, Kosloske AM: Necrotizing fascitis in children: Prompt recognition and aggressive therapy improve survival. *J Pediatr Surg* 1996; 31:1142˘1146
20. Centers for Disease Control and Prevention: Guidelines for the Prevention of Intravascular Catheter-Related Infections. *MMWR* 2002; 51:1˘29
21. 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
22. Choi PTL, Yip G, Quinonez LG, et al: Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* 1999; 27:200˘210
23. Cook D, Guyatt G: Colloid use for fluid resuscitation: Evidence and spin. *Ann Intern Med* 2001; 135:205˘208
24. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: A systematic review of randomized trials. *BMJ* 1998; 316:961˘964
25. Hollenberg SM, Ahrens TS, Astiz ME, et al: Practice parameters for hemodynamic support of sepsis in adult patients. *Crit Care Med* 1999; 27:639˘660
26. 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
27. Regnier B, Rapin M, Gory G, et al: Haemodynamic effects of dopamine in septic shock. *Intensive Care Med* 1977; 3:47˘53
28. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826˘1831

29. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758˜2765
30. 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
31. 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
32. Kellum J, Decker J: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001; 29:1526˜1531
33. Sharshar T, Blanchard A, Paillard M, et al: Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752˜1758
34. Holmes CL, Patel BM, Russell JA, et al: Physiology of vasopressin relevant to management of septic shock. *Chest* 2001; 120:989˜1002
35. Malay MB, Ashton RC, Landry DW, et al: Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699˜705
36. 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
37. 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
38. 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
39. 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
40. 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
41. 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
42. Annane D, Sebille V, Troche G, et al: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; 283:1038˜1045
43. Annane D, Cavaillon JM: Corticosteroids in sepsis: From bench to bedside? *Shock* 2003; 20:197˜207
44. Marik PE, Zaloga GP: Adrenal insufficiency during septic shock. *Crit Care Med* 2003; 31:141˜145
45. Cooper MS, Stewart PM: Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348:727˜734
46. Keh D, Boehnke T, Weber-Carstens S, et al: Immunologic and hemodynamic effects of low-dose*f* hydrocortisone in septic shock: A double-blind, randomized, placebocontrolled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512˜520
47. Bone RC, Fisher CJ, Clemmer TP: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653˜658
48. Cronin L, Cook DJ, Carlet J, et al: Corticosteroid treatment for sepsis: A critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995; 23:1430˜1439
49. The Veterans Administration Systemic Sepsis Cooperative Study Group: Effect on high-dose glucocorticoid therapy on mortality in patients with clinical signs of sepsis. *N Engl J Med* 1987; 317:659˜665
50. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699˜709
51. 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
52. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024˜3029
53. Lorente JA, Landín L, De Pablo R, et al: Effects of blood transfusion on oxygen transport variables in severe sepsis. *Crit Care Med* 1993; 21:1312˜1318
54. 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
55. Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA* 2002; 288:2827˜2835
56. Practice parameter for the use of freshfrozen plasma, cryoprecipitate, and platelets. Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guidelines Development Task Force of the College of American Pathologists. *JAMA* 1994; 271:777˜781
57. Guidelines for red blood cell and plasma transfusion for adults and children. Report of the Working Group. *CMAJ* 1997; 156(Suppl):S1˜S24
58. Practice guidelines for blood component therapy. A report by the American Society of Anaesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 1996; 84:732˜747
59. Warren BL, Eid A, Singer P, et al: High-dose antithrombin III in severe sepsis. A randomized controlled trial. *JAMA* 2001; 286:1869˜1878
60. 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
61. 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. Pressure-and Volume-Limited Ventilation Strategy Group. *N Engl J Med* 1998; 338:355˜361
62. Brochard L, Roudat-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831˜1838
63. 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
64. Brower RG, Fessler HE: Mechanical ventilation in acute lung injury and acute respiratory distress syndrome. *Clin Chest Med* 2000; 21:491˜510
65. 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

66. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301˘1308
67. Hickling KG, Walsh J, Henderson S, et al: Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia:A prospective study. *Crit Care Med* 1994; 22:1568˘1578
68. Bidani A, Tzouanakis AE, Cardenas VJ, et al: Permissive hypercapnia in acute respiratory failure. *JAMA* 272:957˘962
69. Marini JJ, Ravenscraft SA: Mean airway pressure: Physiologic determinants and clinical importance Part I: Physiologic determinants and measurements. *Crit Care Med* 1992; 20:1461˘1472
70. 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
71. 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
72. Stocker R, Neff T, Stein S, et al: Prone positioning and low-volume pressurelimited ventilation improve survival in patients with severe ARDS. *Chest* 1997; 111:1008˘1017
73. Lamm WJ, Graham MM, Albert RK: Mechanism by which prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994; 150:184˘193
74. 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
75. 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
76. Chatte G, Sab JM, Dubois JM, et al: Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; 155:473˘478
77. Drakulovic M, Torres A, Bauer T, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999; 354:1851˘1858
78. Esteban A, Alia I, Tobin MJ, et al: Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1999; 159:512˘518
79. Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; 335:1864˘1869
80. Esteban A, Alia I, Gordo F, et al: Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med* 1997; 156:459˘465
81. 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
82. 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
83. 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
84. Giostra E, Magistris MR, Pizzolato G, et al: Neuromuscular disorder in intensive care unit patients treated with pancuronium bromide. Occurrence in a cluster group of seven patients and two sporadic cases, with electrophysiologic and histologic examination. *Chest* 1994; 106:210˘220
85. Rossiter A, Souney PF, McGowan S, et al: Pancuronium-induced prolonged neuromuscular blockade. *Crit Care Med* 1991; 19:1583˘1587
86. Partridge BL, Abrams JH, Bazemore C, et al: Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. *Crit Care Med* 1990; 18:1177˘1179
87. Vanderheyden BA, Reynolds HN, Gerold KB, et al: Prolonged paralysis after longterm vecuronium infusion. *Crit Care Med* 1992; 20:304˘307
88. 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
89. Manthous CA, Chatila W: Prolonged weakness after withdrawal of atracurium. *Am J Respir Crit Care Med* 1994; 150:1441˘1443
90. Prielipp RC, Coursin DB, Scuderi PE, et al: Comparison of the infusion requirements and recovery profiles of vecuronium and cisatracurium 51W89 in intensive care unit patients. *Anesth Analg* 1995; 81:3˘12
91. Brandom BW, Yellon FF, Lloyd ME, et al: Recovery from doxacurium infusion administered to produce immobility for more than four days in pediatric patients in the intensive care unit. *Anesth Analg* 1997; 84:307˘314
92. 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; 25:25575˘25583
93. 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
94. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359˘1367
95. Finney SJ, Zekveld C, Elia A, et al: Glucose control and mortality in critically ill patients. *JAMA* 2003; 2041˘2047
96. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med* 2003; 31:359˘366
97. Klein S, Kinney J, Jeejeebhoy K, et al: Nutrition support in clinical practice: Review of published data and recommendations for future research directions. A summary of a conference sponsored by the National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *Am J Clin Nutr* 1997; 66:683˘706
98. 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
99. Kellum J, Angus DC, Johnson JP, et al: Continuous versus intermittent renal replacement therapy: A meta-analysis. *Intensive Care Med* 2002; 28:29˘37

100. 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
101. 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
102. Cade JF: High risk of the critically ill forvenous thromboembolism. *Crit Care Med* 1982; 10:448˘450
103. Belch JJ, Lowe GD, Ward AG, et al: Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 1981; 26:115˘117
104. 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. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; 341:793˘800
105. Borrero E, Bank S, Margolis I, et al: Comparison of antacid and sucralfate in the prevention of gastrointestinal bleeding in patients who are critically ill. *Am J Med* 1985;79:62˘64
106. 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
107. 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. Canadian Critical Care Trials Group. *N Engl J Med* 1998; 338:791˘797
108. 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
109. Pollard AJ, Britto J, Nadel S, et al: Emergency management of meningococcal disease. *Arch Dis Child* 1999; 80:290˘296
110. Kanter RK, Zimmerman JJ, Strauss RH, et al: Pediatric emergency intravenous access. Evaluation of a protocol. *Am J Dis Child* 1986; 140:132˘134
111. 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
112. Carcillo JA, Davis AL, Zaritsky A: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; 266:1242˘1245
113. 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
114. Ceneviva G, Paschall JA, Maffei F, et al: Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics* 1998; 102:e19
115. Keeley SR, Bohn DJ: The use of inotropic and afterload-reducing agents in neonates. *Clin Perinatol* 1988; 15:467˘489
116. Roberts JD Jr, Fineman JR, Morin FC III, et al: Inhaled nitric oxide and persistent pulmonary hypertension of the new born. Inhaled Nitric Oxide Study Group. *N Engl J Med* 1997; 336:605˘610
117. 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
118. 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
119. 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
120. Lauterbach R, Pawlik D, Kowalczyk D, et al: Effect of the immunomodulating agent, pentoxifylline, in the treatment of sepsis in prematurely delivered infants: A placebocontrolled, double-blind trial. *Crit Care Med* 1999; 27:807˘814
121. Carcillo JA, Fields AI, American College of Critical Care Medicine Task Force Committee Members: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; 30:1365˘1378
122. De Kleijn ED, Joosten KF, Van Rijn B, et al: Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J* 2002; 21:330˘336
123. 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
124. Min M, U T, Aye M, et al: Hydrocortisone in the management of dengue shock syndrome. Southeast Asian J Trop Med Public *Health* 1975; 6:573˘579
125. Sumarmo, Talogo W, Asrin A, et al: Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics* 1982; 69:45˘49
126. Hazelzet JA, de Kleijn ED, de Groot R: Endothelial protein C activation in meningococcal sepsis. *N Engl J Med* 2001; 345:1776˘1777
127. de Kleijn ED, de Groot R, Hack CE, et al: Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: A randomized, double-blinded, placebo-controlled, dose-finding study. *Crit Care Med* 2003; 31:1839˘1847
128. Bilgin K, Yaramis A, Haspolat K, et al: A randomized trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. *Pediatrics* 2001; 107:36˘41
129. La Gamma EF, De Castro MH: What is the rationale for the use of granulocyte and granulocyte-macrophage colonystimulating factors in the neonatal intensive care unit? *Acta Paediatr Suppl* 2002; 91:109˘116
130. 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
131. 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

132. Alejandria MM, Lansang MA, Dans LF, et al: Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* 2002; (1):CD001090
133. Meyer DM, Jessen ME: Results of extracorporeal membrane oxygenation in children with sepsis. The Extracorporeal LifeSupport Organization. *Ann Thorac Surg* 1997; 63:756˘761
134. Goldman AP, Kerr SJ, Butt W, et al: Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. *Lancet* 1997; 349:466˘469
135. Brochard L, Rauss A, Benito S, et al: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150:896 ˘ 903

Appendix A. 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. Contraindications to use of recombinant human activated protein C (rhAPC)[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

See labeling instructions for relative contraindications.
[a]The committee recommends that platelet count be maintained at ≥30,000 during infusion of rhAPC.
Physicians Desk Reference. 57th Edition. Montvale, NJ, Thompson PDR, 2003, pp 1875˘1876.

Appendix C. ARDSNET Ventilator Management (66)

¸ 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%
¸ Anticipated PEEP settings at various FIO_2 requirements

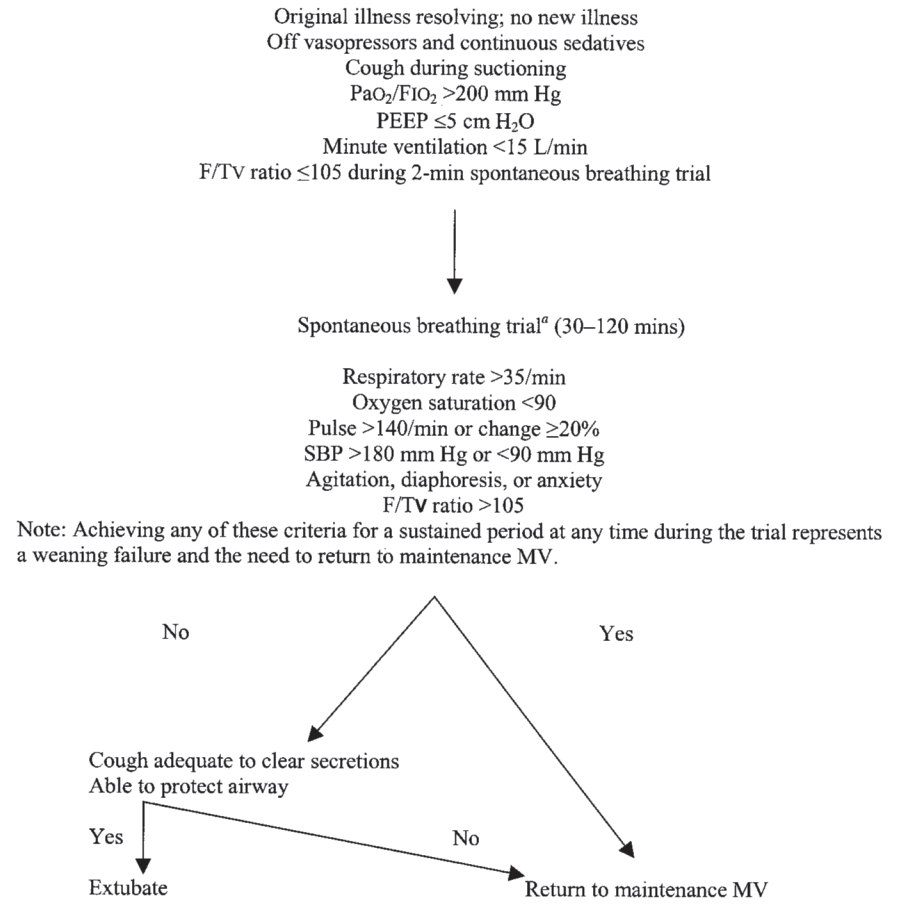
FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20˘24

*Predicted Body Weight Calculation

¸ Male 50 + 2.3 [height (inches) ˘ 60] or 50 + 0.91 [height (cm) ˘ 152.4]
¸ Female 45.5 + 2.3 [height (inches) ˘ 60] or 45.5 + 0.91 [height (cm) ˘ 152.4]

Tv, tidal volume; SaO_2, arterial oxygen saturation; PEEP, positive end-expiratory pressure.

Appendix D. Use of spontaneous breathing trial in weaning ARDS patients



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

[a]Options include T-piece, continuous positive airway pressure 5 cm H_2O, or low-level (5–10 cm H_2O typically based on endotracheal tube size) pressure support ventilation (78–80, 135).