CHEST Postgraduate Education Corner
CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Early Management of Severe Sepsis

Concepts and Controversies

Paul E. Marik, MD

Sepsis is among the most common reasons for admission to ICUs throughout the world, and it is believed to be the third most common cause of death in the United States. The pathogenetic mechanism and physiologic changes associated with sepsis are exceedingly complex, but our understanding is evolving rapidly. The major pathophysiologic changes in patients with septic shock include vasoplegic shock (distributive shock), myocardial depression, altered microvascular flow, and a diffuse endothelial injury. These pathophysiologic changes play a central role in the management of sepsis. The early management of patients with severe sepsis and septic shock centers on the administration of antibiotics, IV fluids, and vasoactive agents, followed by source control. However, the specific approach to the resuscitation of patients with septic shock remains highly controversial. This review provides a practical and physiologic-based approach to the early management of sepsis and explores the controversies surrounding the management of this complex condition.

CHEST 2014; 145(6):1407–1418

Abbreviations: ARISE = Australasian Resuscitation of Sepsis Evaluation; AUC = area under the curve; BUSH = Bathurst-ultrasonic cardiac output monitor hemodynamic; CORTICUS = Corticosteroid Therapy of Septic Shock Study; CVP = central venous pressure; EGDT = Early Goal Directed Therapy; EVLW = extravascular lung water; MAP = mean arterial pressure; $Scvo_2$ = central venous oxygen saturation; USCOM = ultrasonic cardiac output monitor; VASST = Vasopressin in Septic Shock Trial

The word "sepsis" is derived from the ancient Greek word for rotten flesh and putrefaction. Sepsis refers to the systemic inflammatory response following microbial infection.[1] Although the clinical criteria that defines sepsis remain controversial,[1-4] sepsis may best be defined as the "systemic response to infection with the presence of some degree of organ dysfunction."[3] Sepsis is among the most common reasons for admission to ICUs throughout the world. An epidemiologic study in European ICUs demonstrated an incidence of 37% for sepsis and 30% for severe sepsis.[5] Although the exact incidence of sepsis in the United States is unclear, the annualized incidence has been reported to have increased by 8.7% to 13% over the past 30 years.[6-9] The aging of the population in developed countries is believed to be largely responsible for the increasing incidence of sepsis.[10] Epidemiologic data from 2004 to 2009 demonstrated a decrease in in-hospital mortality from 35% to 26%.[6] This study estimated that there were 229,044 deaths from severe sepsis in 2009, which would place severe sepsis as the third most common cause of death in the United States, after heart disease and malignant neoplasms.[6] The 1-year all-cause mortality of patients treated for severe sepsis and septic shock may be as high as 44%.[11] In addition, some data suggest that patients who have had a septic episode are at an increased risk of death for up to 5 years following the acute event.[12]

Sepsis is an exceedingly complex condition. Exposure of human macrophages to bacterial antigens has been demonstrated to result in a significant change in the expression of over 950 genes.[13] These include genes for proinflammatory and antiinflammatory cytokines, chemokines, adhesion molecules, transcription factors, enzymes, clotting factors, stress proteins, and antiapoptotic molecules. These gene products alter the

Manuscript received September 5, 2013; revision accepted December 15, 2013.
Affiliations: From the Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, Norfolk, VA.
Correspondence to: Paul Marik, MD, Eastern Virginia Medical School, 825 Fairfax Ave, Ste 410, Norfolk, VA 23507; e-mail: marikpe@evms.edu

DOI: 10.1378/chest.13-2104

function of every cell and tissue in the body. Furthermore, these mediators interact in complex positive and negative feedback loops and result in epigenetic modifications that further alter the expression of this network of mediators.[14] The early phase of sepsis is generally believed to result from the uncontrolled production of proinflammatory mediators, the so-called "cytokine storm."[15] However, some data suggest that both a proinflammatory and an opposing antiinflammatory response occur concurrently in patients with sepsis.[16,17] In general, following a variable time course, patients transition from a predominantly proinflammatory to an antiinflammatory immunosuppressive state.[14,17,18]

The pathogenetic mechanism and physiologic changes associated with sepsis are exceedingly complex, but our understanding of this topic is evolving rapidly; the reader is referred to excellent reviews on this topic.[4,14-19] The major pathophysiologic changes in patients with severe sepsis and septic shock include vasoplegic shock (distributive shock), myocardial depression, altered microvascular flow, and a diffuse endothelial injury.[20,21] These pathophysiologic changes play a central role in the early management of patients with sepsis. The widespread endothelial injury results in a microvascular leak, with tissue and organ edema, hypotension, and shock. Increased endothelial permeability is caused by shedding of the endothelial glycocalyx and the development of gaps between endothelial cells (paracellular leak).[22,23] Vasoplegic shock due to the failure of the vascular smooth muscle to constrict, results in arterial and venodilatation.[20] Venodilatation decreases venous return and compounds the intravascular volume deficit caused by the vascular leak. This review focuses on those interventions that are currently believed to improve the outcome of patients with severe sepsis. Experimental immunomodulating interventions, including the use of novel molecules and antibodies,[14] extracorporeal blood purification,[24] or approaches to "seal" the leaky endothelium,[23] are not discussed.

The early management of patients with sepsis centers on the administration of antibiotics, IV fluids, and vasoactive agents, followed by source control. Unfortunately, there is no high-quality evidence (from one or more randomized controlled trials) demonstrating that any of these interventions alters outcome. However, it is likely that the early detection of sepsis with the timely administration of appropriate antibiotics is the single most important factor in reducing morbidity and mortality from sepsis.[25] It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ failure and a higher mortality.[26,27] Physicians, therefore, need to have a high index of suspicion for the presence of sepsis. The clinical features that should heighten the index of suspicion for the diagnosis of sepsis are listed in Table 1.

Antibiotic Therapy

Empirical IV antibiotic therapy should be started as soon as possible and within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. In a retrospective analysis of 2,600 patients, Kumar and colleagues[28] demonstrated that the risk of dying increased progressively with an increase in the time to receipt of the first dose of antibiotic from the onset of sepsis-induced hypotension. Furthermore, there was a 5% to 15% decrease in survival with every hour of delay over the first 6 h. The choice of antibiotics is largely determined by the source or focus of infection, the patient's immunologic status, whether the infection is nosocomial or community acquired, and knowledge of the local microbiology and sensitivity patterns. Initial empirical antiinfective therapy should include one or more drugs act against the likely pathogens and that penetrate into the presumed source of sepsis. Because the identity of the infecting pathogen(s) and its sensitivity pattern(s) are unknown at the time of initiation of antibiotics, the initial regimen in patients with severe sepsis and septic shock should include two or more antibiotics or an extended spectrum β-lactam antibiotic with the aim of treating all realistically possible microbial causes. A number of studies have demonstrated that appropriate initial antimicrobial therapy, defined as the use of at least one antibiotic active in vitro against the causative bacteria, reduced mortality when compared with the inappropriate therapy other patients received.[29-31]

Once a pathogen is isolated, monotherapy is adequate for most infections; this strategy of initiating broad-spectrum cover with two or more antibiotics, and then narrowing the spectrum to a single agent when a pathogen is identified, is known as "antimicrobial

Table 1—*Clinical Features That Should Alert the Physician to the Diagnosis of Severe Sepsis*

Clinical Feature
Heart rate > 120/min
Systolic BP < 90 mm Hg
Respiratory rate > 20/min
Temperature > 38.5° or < 36° C
Confusion
Lactate > 2 mmol/L
Procalcitonin > 0.5 ng/mL
WBC count > 12,000 or < 4,000 cells/μL
Band count > 5%
Lymphocytopenia < 0.5×10^3 μL
Thrombocytopenia < 150×10^3 μL
Oliguria
Chills and rigors

de-escalation."[32] The indications for continuation of double-antimicrobial therapy include enterococcal infections and severe intraabdominal infections. In addition, double antimicrobial therapy (third-generation cephalosporin and macrolide) is recommended for patients with severe community-acquired pneumonia and those with pneumococcal bacteremia.[33-35] To rapidly achieve adequate blood and tissue concentrations, antibiotics should be given via IV, at least initially. Dosing regimens should take into account whether the antibiotic "kills" by time-dependent kinetics (eg, β-lactam antibiotics, vancomycin) or by concentration-dependent kinetics (eg, aminoglycoside).[30,31,36,37] The clinical effectiveness of β-lactam antibiotics and vancomycin is optimal when the concentration of the antimicrobial agent in the serum exceeds the minimum inhibitory concentration of the infecting organism for at least 40% of the dosing interval. In addition, antibiotic dosing should take into account the patient's hepatic and renal function.

Fluid Therapy

Beyond the early administration of antibiotics, aggressive "supportive measures" may be harmful and the "less is more" paradigm appears applicable for the management of patients with severe sepsis. In these highly vulnerable patients, more intensive treatment may promote the chance of unwanted adverse effects and, hence, iatrogenic injury.[38] Current teaching suggests that aggressive fluid resuscitation is the best initial approach for the cardiovascular instability of sepsis. Consequently, large volumes of fluid (5-10 L) are often infused in the early stages of sepsis. There is, however, no human data that substantial (>30 mL/kg) fluid resuscitation reliably improves BP or end-organ perfusion.[39,40]

From a pathophysiologic point of view, large-volume fluid resuscitation in patients with sepsis is illogical and may worsen the hemodynamic derangements of sepsis. In patients with septic shock who are fluid responders (an increase in cardiac output with fluid boluses), vasodilatation with a fall in systematic vascular resistance has been observed.[41,42] A similar finding has been noted in an experimental sepsis model.[43] Hence, although the cardiac output increases, vasodilatation occurs and the BP may remain unchanged.[41] Increased shear stress increases the expression of nitric oxide synthetase with increased release of nitric oxide.[20] In addition, increased cardiac filling pressures increase the release of natriuretic peptides, which act synergistically with nitric oxide, causing cyclic guanosine monophosphate-mediated vasodilatation.[20] Endotoxin enhances this vasodilatory response.[44] As cardiac filling pressures increase, extravascular lung water (EVLW) and tissue edema increase.[45]

Furthermore, increased cardiac filling pressures consequent to large-volume resuscitation increase the release of natriuretic peptides.[46,47] Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx.[48-50] The endothelial glycocalyx plays a major role in regulating endothelial permeability, and damage to the glycocalyx plays a major role in increasing tissue edema.[51] Because of the endothelial injury, capillary leak, and increased hydrostatic pressures, <5% of infused crystalloid remains intravascular within 3 h after infusion, resulting in an increase in EVLW and further tissue edema.[52] Increased EVLW has been demonstrated to be a strong independent predictor of death.[53-55] In patients with pneumonia, large-volume fluid resuscitation may result in severe pulmonary edema. Myocardial edema due to excess fluid administration compounds the myocardial dysfunction.[43] Evidence of the harmful effects of aggressive fluid resuscitation on the outcome of sepsis is supported by experimental studies as well as by data accumulated from clinical trials.[43,56] Multiple clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patient with sepsis.[5,54,57-59] In a secondary analysis of the Vasopressin in Septic Shock Trial (VASST), Boyd and colleagues[60] demonstrated that a greater positive fluid balance and a higher central venous pressure (CVP) at both 12 h and 4 days were independent predictors of death. In a recent study, Micek and colleagues[61] demonstrated that a positive fluid balance at 8 days was the strongest independent predictor of hospital mortality. In this study, the 24-h fluid balance was 37.5 mL/kg (about 2.5 L) in the survivors compared with 55.3 mL/kg (3.9 L) in those who died. Zhang and colleagues[47] demonstrated a strong correlation among the net fluid balance, the increase in brain natriuretic peptide, and death in patients with sepsis. The most compelling data that fluid loading in sepsis is harmful come from the Fluid Expansion as Supportive Therapy (FEAST) study performed in 3,141 sub-Saharan children with severe sepsis.[62] In this study, aggressive fluid loading was associated with a significantly increased risk of death. Furthermore, there was no subgroup of patients that benefited from aggressive fluid resuscitation. This study is frequently dismissed with the argument that it cannot be extrapolated to adult patients.[40]

In contemporary sepsis studies, between 1.5 and 4.0 L of fluid were given in the first 24 h.[47,61,63] This compares to 4.9 ± 2.9 and 13.4 ± 6.3 L at 6 and 72 h, respectively, in the intervention arm of the Early Goal Directed Therapy (EGDT) study.[64] In the Australasian Resuscitation of Sepsis Evaluation (ARISE) study, which used the same entry criteria as the EGDT study, 2.2 ± 1.9 L of fluid were given in the first 6 h.[63]

The hospital mortality was 23% in the ARISE study compared with 30% in the intervention arm of the EGDT study. In the VASST, optimal survival occurred with a positive fluid balance of approximately 3 L at 12 h.[60] In some patients, hypotension and tachycardia do resolve with limited fluid resuscitation. However, fluids alone will not reverse the hemodynamic instability of patients with more severe sepsis; in these patients, fluids alone are likely to exacerbate the vasodilatory shock and increase the capillary leak and tissue edema. Based on these data, I suggest limiting the initial fluid resuscitation to approximately 20 to 30 mL/kg. Furthermore, I recommend this fluid be given as 500-mL fluid challenges. It is important to emphasize that this conservative approach to fluid management in patients with sepsis is based on indirect evidence and not on a randomized controlled trial specifically designed to answer this question. Furthermore, this recommendation differs somewhat from that of the most recent Surviving Sepsis Campaign guidelines, which suggest "a minimum fluid challenge of 30ml/kg" and that "greater amounts of fluid may be needed in some patients (Grade 1C)."[65]

The optimal time to start a vasopressor agent in patients with sepsis has not been well studied. However, after receiving 20 to 30 mL/kg of crystalloid, it seems unlikely that additional fluid boluses will increase the mean arterial pressure (MAP) in patients who remain hypotensive.[39,40] I would, therefore, recommend the initiation of a vasopressor agent (norepinephrine) in patients who remain hypotensive (MAP < 65 mm Hg) after receiving 20 to 30 mL/kg of crystalloid solution. Additional fluid boluses (500 mL) may be given once the "target" norepinephrine dose is achieved (about 0.1-0.2 μg/kg/min), and this should be based on a dynamic assessment of volume responsiveness and ventricular function (Fig 1). I suggest using the passive leg-raising maneuver coupled with minimally invasive cardiac output monitoring to assess volume responsiveness.[66,67] Calibrated pulse contour analysis, bioreactance, the ultrasonic cardiac output monitor (USCOM), carotid Doppler flow, Doppler echocardiography, or esophageal Doppler techniques can be used to dynamically follow the cardiac output in real time.[68-72] Bioreactance, USCOM, and carotid Doppler flow are truly noninvasive and are suitable for guiding fluid resuscitation in the ED.[72-77] In cases of life-threatening hypotension (diastolic BP < 40 mm Hg), treatment with vasopressors should be started concurrently with fluid administration.[78]

Recent data suggest that the choice of resuscitation fluid may have an effect on outcome. Balanced salt solutions (Lactated Ringers solution, Hartmann's solution, Plasmalyte 148) are the preferred resuscitation fluids. Normal saline (0.9% NaCl) is associated with an increased risk of renal dysfunction,[79] a hyperchloremic metabolic acidosis, and an increased risk of death.[80-82] Similarly, hydroxyethyl starch solutions are associated with an increased risk of renal failure and death and are considered contraindicated in patients with sepsis.[83,84] Albumin has a number of theoretical benefits in patients with sepsis, including its antioxidant and antiinflammatory effects as well as its ability to stabilize the endothelial glycocalyx.[85,86] However, the use of albumin in patients with sepsis is controversial. The multicenter randomized Albumin Italian Outcome Sepsis Study (ALBIOS) demonstrated that a 25% albumin infusion decreased the mortality of patients with septic shock (and a serum albumin of < 3g/dL) once hemodynamic stability had been achieved.[87] The use of albumin is patients with sepsis is supported by the Saline vs Albumin Fluid Evaluation (SAFE) study, as well as by a metaanalysis on this topic.[88-90] Because a 25% albumin infusion may restore the damaged endothelial glycocalyx, this would appear to be a reasonable intervention in patients with severe septic shock.[85,86]

Vasopressors and Inotropic Agents

A low MAP is a reliable predictor for the development of organ dysfunction. When the MAP falls below an organ's autoregulatory threshold, organ blood flow decreases in an almost linear fashion.[91] Because the autoregulatory ranges of the heart, brain, and kidney are > 60 mm Hg,[91] a MAP below this level will likely result in organ ischemia. An analysis of a large ICU database demonstrated that the risk of kidney injury and death increased sharply as the MAP fell below 60 mm Hg.[92] Varpula and colleagues[93] studied the hemodynamic variables associated with mortality in patients with septic shock. These researchers calculated the area under the curve (AUC) of various MAP thresholds over a 48-h time period. The highest AUC values were found for a MAP < 65 mm Hg (AUC, 0.83; 95% CI, 0.772-0.934). Because of the shift in the autoregulatory range (to the right) in patients with chronic hypertension, a higher MAP may be required in these patients.

The Assessment of Two Levels of Arterial Pressure on Survival in Patients With Septic Shock (SEPSISPAM) is a multicenter, randomized controlled trial completed in France.[94] In this study, patients with septic shock were randomized to achieve a target MAP of 65 to 70 or 80 to 85 mm Hg. The primary outcome was 28-day mortality. Secondary outcomes included 90-day mortality and organ failures. A priori, a secondary analysis was planned in patients with and without a history of hypertension. Overall, there was no difference in either primary or secondary end point between the two treatment groups. However the incidence of organ failures (particularly renal dysfunction) was

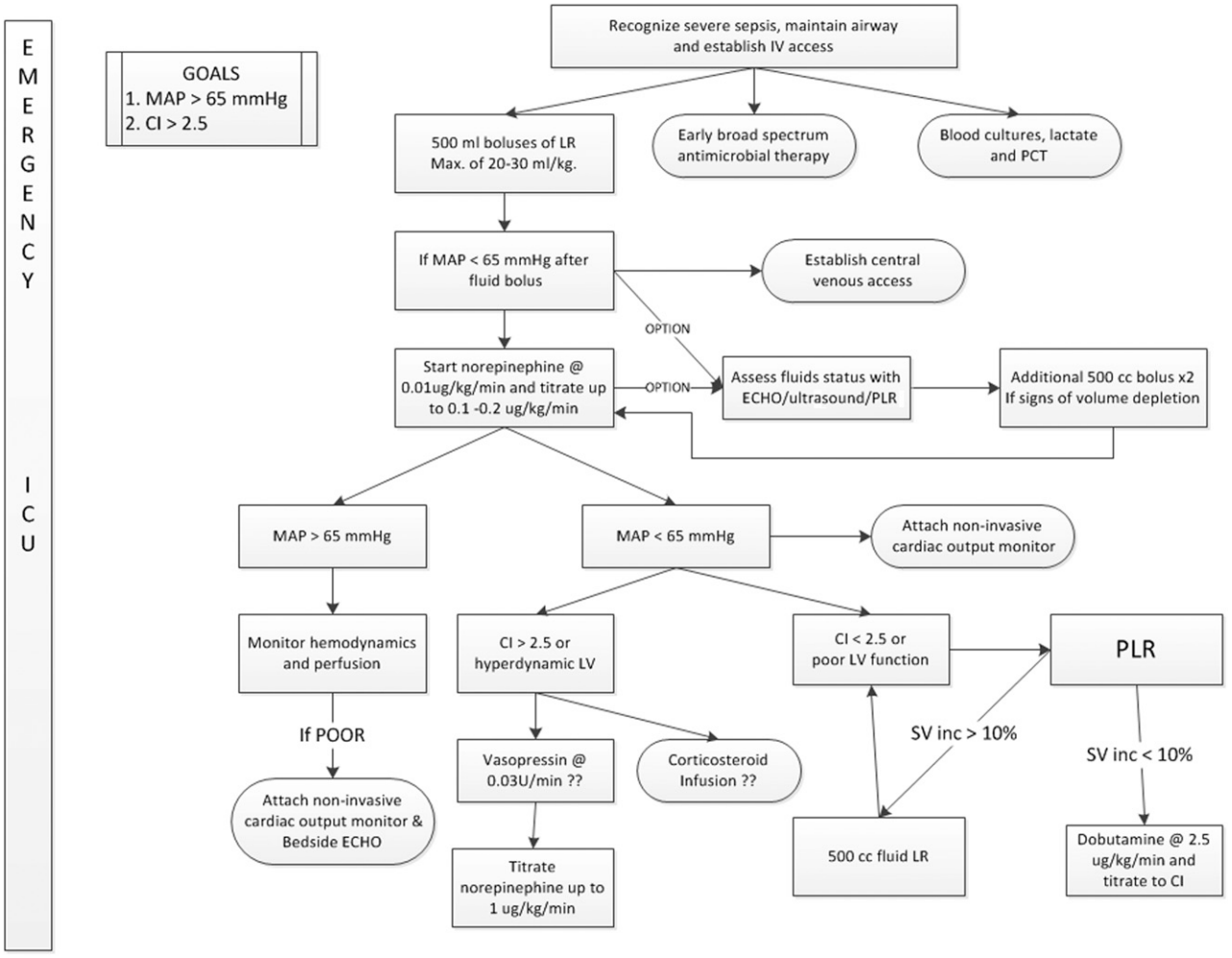

FIGURE 1. Suggested initial approach to the management of patients with severe sepsis and septic shock. CI = cardiac index; ECHO = echocardiography; inc = increase; LR = Lactated Ringers solution; LV = left ventricle; MAP = mean arterial pressure; Max = maximal; PCT = procalcitonin; PLR = passive leg raising; SV = stroke volume.

higher in the subgroup of patients with chronic hypertension in the lower MAP group. Furthermore, much like the Varpula study, the time below the 65 mm Hg (but not 80 mm Hg) threshold was an independent predictor of death. Based on these data, I suggest targeting an initial MAP of 65 mm Hg in patients with septic shock. In those patients with a history of chronic hypertension, I would suggest targeting a slightly higher MAP (75-80 mm Hg).[95]

In patients with sepsis, norepinephrine increases BP as well as cardiac output and renal, splanchnic, cerebral, and microvascular blood flow, while minimally increasing heart rate.[96-98] Although not widely appreciated, norepinephrine causes α_1 adrenergic receptor-mediated venoconstriction; this increases the mean systemic pressure with a significant increase in venous return and cardiac preload.[99,100] The early use of norepinephrine restores BP and organ blood flow with a significant fluid sparing effect. Hamzaoui and colleagues[101] demonstrated that the early administration of norepinephrine largely reverses the hemodynamic abnormalities of severe vasodilatory shock. Abid and colleagues[102] demonstrated that the early use of norepinephrine in patients with septic shock was a strong predictor of survival. In situations in which norepinephrine is not available, epinephrine is a suitable alternative agent.[103,104] In patients with septic shock, dopamine is associated with an increased mortality when compared with norepinephrine, and is best avoided.[105,106] Similarly, phenylephrine is not recommended, because in experimental models it decreases cardiac output as well as renal and splanchnic blood flow.[107] Furthermore, phenylephrine has not been well studied in patients with sepsis.

In patients who remain hypotensive or have evidence of inadequate organ perfusion despite fluid optimization and an adequate dose of norepinephrine (approximately 0.1-0.2 μg/kg/min), I recommend further hemodynamic assessment to exclude ventricular dysfunction. Global biventricular dysfunction has

been reported in up to 60% of patients with septic shock.[108,109] Ventricular function is best assessed by bedside echocardiography and confirmed by minimally invasive cardiac output monitoring. Dobutamine at a starting dose of 2.5 μg/kg/min is recommended in patients with significant ventricular dysfunction (milrinone is an alternative agent).[108] The dose of dobutamine should be titrated to the hemodynamic response as determined by minimally invasive cardiac output monitoring.[108,110] This recommendation is in keeping with the updated Surviving Sepsis Campaign guidelines, which suggest "a trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C)."[65] These recommendations, however, differ from the EGDT study protocol, which suggests the use of an inotropic agent based on the CVP (>8-12 mm Hg) and a central venous oxygen saturation ($Scvo_2$) of <70% (without an evaluation of ventricular function or cardiac output).[64] Bouferrache and colleagues[111] demonstrated a poor agreement in the use of inotropic agents when treatment was guided by early transesophageal echocardiography as compared with the EGDT study protocol in patients presenting with septic shock.

The Surviving Sepsis Campaign guidelines suggest that "vasopressin 0.03 units/min can be added to norepinephrine with the intent of either raising MAP or decreasing norepinephrine dosage (ungraded)."[65] Vasopressin reverses the "relative vasopressin deficiency" seen in patients with septic shock and increases adrenergic sensitivity.[20,112] Terlipressin is an alternative agent should vasopressin not be available (terlipressin is not Food and Drug Administration-approved in the United States).[113,114] Vasopressin may be effective in raising BP in patients with refractory hypotension; however, the optimal time to initiate this drug is not clear. The VASST randomized patients with septic shock to norepinephrine alone or norepinephrine plus vasopressin at 0.03 units/min.[115] By intention-to-treat analysis there was no difference in outcome between the groups. However, an a priori-defined subgroup analysis demonstrated that survival among patients receiving <0.2 μg/kg/min norepinephrine at the time of randomization was better with the addition of vasopressin than that of those receiving norepinephrine at a dose >0.2 μg/kg/min. I, therefore, suggest the addition of vasopressin at a dose of norepinephrine between 0.1 and 0.2 μg/kg/min. Thereafter the dose of norepinephrine should be titrated to achieve a MAP of at least 65 mm Hg. It is important to emphasize that vasopressin is administered as a fixed dose of 0.03 units/min and should not be uptitrated. An outline of this treatment algorithm for the hemodynamic stabilization of patients with septic shock is provided in Fig 1.

Although this algorithm/protocol has not been tested in a randomized controlled trial, it is very similar to the Bathurst-USCOM hemodynamic (BUSH) protocol developed by Smith and colleagues.[116] Using data from the Australian and New Zealand Intensive Care Society (ANZICS) Center for Outcomes and Resource Evaluation (CORE) database, these researchers demonstrated a 94% reduction in mortality from septic shock with the introduction of the BUSH protocol.[116] Patients treated with the BUSH protocol received significantly less fluid in the first 24 and 48 h, whereas a greater percentage received norepinephrine within the first 24 h as compared with the control group. It is important, however, to emphasize that "patients are not airplanes and doctors are not pilots"[117]; each patient is unique, with a unique response to invading pathogens and a unique response to treatment. Therefore, these algorithms must be adapted dynamically to each patient as his/her clinical course evolves.

Resuscitation End Points

A large number of hemodynamic, perfusion, oxygenation, and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock.[65,111,118] Most of these targets, however, are controversial and are not supported by outcome data. The Surviving Sepsis Campaign guidelines recommend a CVP of 8 to 12 mm Hg (12-15 mm Hg if mechanically ventilated), an $Scvo_2$ >70%, and a urine output >0.5 mL/kg/h as targets for resuscitation.[65] It has been well established that there is no relationship between the CVP and intravascular volume and no relationship between the CVP and fluid responsiveness.[119,120] Consequently, I believe that the CVP should not be used to guide fluid therapy.[66]

The use of $Scvo_2$ to guide the resuscitation of patients who are septic is equally problematic. Patients who are septic usually have a normal or increased $Scvo_2$ caused by reduced oxygen extraction.[121,122] Indeed, in the recent review article by Angus and van der Poll,[4] a $Scvo_2$ >70% was considered a diagnostic criterion for severe sepsis. In a large, multicenter, goal-directed study conducted by Pope and colleagues,[123] a high (>90%) but not a low (<70%) initial $Scvo_2$ was an independent predictor of death. Furthermore, in a paper by Nee and Rivers,[124] which reviewed the outcome of patients enrolled in the Surviving Sepsis Campaign database, they conclude that the "attainment of a CVP of >8 mm Hg and $Scvo_2$ of >70% did not influence survival in patients with septic shock."[124] Although urine output may be a valuable marker of

renal perfusion in hypovolemic states, this clinical sign becomes problematic in sepsis-associated acute kidney injury; experimental models show that oliguria occurs in the presence of marked global renal hyperemia.[125-127] Titration of fluids to urine output may, therefore, result in fluid overload. Three large, international, multicenter, randomized trials (ProCESS, ARISE, and ProMISe) are investigating the role of the CVP and $ScvO_2$ as targets for therapy in patients with severe sepsis and septic shock.[128] It is hoped that the outcome of these trials will resolve this ongoing controversy.[129] In addition, two trials are evaluating the role of noninvasive hemodynamic monitors in guiding fluid resuscitation in the early stages of septic shock.[76,77]

The Surviving Sepsis Campaign guidelines recommend "targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion."[65] This recommendation is based on the notion that an elevated lactate is a consequence of tissue hypoxia and inadequate oxygen delivery,[4] and is "supported" by two studies that used lactate clearance as the target of resuscitation.[130,131] However, the concept that sepsis is associated with tissue hypoxia is unproven and likely incorrect, as argued by Hotchkiss and Karl[132] >20 years ago. Multiple studies have demonstrated that the increased blood lactate concentration in sepsis is not caused by tissue hypoxia but is rather produced aerobically as part of the metabolic stress response.[133-136] Increasing oxygen delivery in these patients does not increase oxygen consumption.[135-137] Previous studies have demonstrated that targeting supramaximal oxygen delivery does not improve outcome and may be harmful.[138,139] Morelli and colleagues[140] demonstrated that in the setting of septic shock, an infusion of a short-acting β-blocker reduced cardiac output and oxygen delivery; paradoxically, this intervention reduced blood lactate levels and improved patient survival as compared with the control group.

These data would suggest that achieving a MAP of at least 65 mm Hg should be the primary target in the resuscitation of patients with septic shock. Furthermore, although attempts to achieve a supranormal cardiac index may be potentially harmful, I would suggest targeting a normal cardiac index (>2.5 L/min/m^2).[138] Although a falling arterial lactate concentration is a sign that the patient is responding to therapy (attenuation of the stress response), titrating therapy to a lactate concentration is devoid of scientific evidence.[135,136] Additional end points of resuscitation remain unproven at this time.

Blood Transfusion

The 2012 Surviving Sepsis Campaign guidelines state that "during the first 6 hours of resuscitation, if $ScvO_2$ is less than 70%...then dobutamine infusion…or transfusion of packed red blood cells to achieve a hematocrit of greater than or equal to 30% in attempts to achieve the $ScvO_2$ goal are options."[65] In patients who are septic, RBC transfusions do not acutely increase tissue oxygen uptake; paradoxically, they have been demonstrated to impair microcapillary flow and tissue oxygenation.[137] In addition, the release of cell-free hemoglobin from banked blood may be particularly deleterious in patients who are septic.[141,142] One study demonstrated that "transfusion of PRBCs was associated with worsened clinical outcomes in patients with septic shock treated with EGDT."[143] Blood transfusions are associated with an increased risk of secondary infections, multiorgan dysfunction syndrome, and death and should be considered only in patients with a hemoglobin <7 g/dL.[144,145]

Corticosteroids

The use of low-dose corticosteroids in patients with severe sepsis remains controversial.[146] It has been proposed that inadequate cellular glucocorticoid activity (critical illness-related corticosteroid insufficiency) due to either adrenal suppression or glucocorticoid tissue resistance results in an exaggerated and protracted proinflammatory response.[147] In addition to down-regulating the proinflammatory response, corticosteroids may have additional beneficial effects, including increasing adrenergic responsiveness[148] and preserving the endothelial glycocalyx.[149] Because corticosteroids enhance local immune defenses but reduce global nuclear factor κB expression and cause a predominant TH2 immunosuppressive state, steroids are likely to be beneficial early in the course of the disease but are likely to compound the immunosuppression when given later in the course of sepsis. The time-dependent initiation of the use of corticosteroids has not been taken into consideration in those studies (and meta-analyses) which have analyzed the benefits/risk of steroids in sepsis. Park and colleagues,[150] in a retrospective analysis of 178 patients with septic shock, found that corticosteroids were only of benefit if given within 6 h after the onset of septic shock-related hypotension. In the Corticosteroid Therapy of Septic Shock Study (CORTICUS), the initial time frame for the initiation of corticosteroids was 24 h, which was then increased to 72 h.[151] It is also important to recognize that in the CORTICUS, >60% of the patients were surgical patients. It has now been well established that surgery induces an immunosuppressive TH2 state and that this occurs within hours of surgery.[152] Postsurgical patients who develop sepsis remain in a predominant TH2 state.[152] It would, therefore, appear counterproductive to give postsurgical patients who are septic corticosteroids because this

is only likely to compound the immunosuppressive state and increase the risk of secondary infections (as was demonstrated in the CORTICUS).

Although the mortality benefit of corticosteroids in septic shock is controversial, low-dose hydrocortisone has been demonstrated to significantly reduce vasopressor dependency, with a favorable side-effect profile.[146,153] Furthermore, the combination of low-dose corticosteroids and vasopressin has been associated with decreased mortality and organ dysfunction in patients with septic shock.[154-156] Based on these data, I would suggest treatment with hydrocortisone concomitant with the initiation of vasopressin for the management of severe vasodilatory septic shock; however, this approach has not been tested prospectively. Two large randomized controlled trials are currently underway, and it is hoped that they will resolve this ongoing controversy about the use of corticosteroids in septic shock.[157,158]

Source Control

It has been known for centuries that, unless the source of the infection is controlled, the patient cannot be cured of his/her infective process and death will eventually ensue. It is important that specific diagnoses of infection that require emergent source control be made in a timely manner (eg, necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) and surgical consultation be obtained immediately.[65,159] When source control in a patient who is severely septic is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess).[65,160] If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.[161]

Conclusions

Despite initial enthusiasm about "disease-modifying agents," the early administration of appropriate antibiotics and early hemodynamic resuscitation remain the cornerstone of the management of patients with sepsis. I believe that the first step in the resuscitation of a patient with septic shock is to achieve a MAP of at least 65 mm Hg with the use of vasoactive agents and small volumes of balanced fluid. A simultaneous goal would be to ensure adequate flow (cardiac output) as determined by echocardiography and minimally invasive cardiac output monitoring, supported by an integrated assessment, which includes physical examination, biochemical measurements, and the monitoring of the patient's clinical response to therapy.

Acknowledgments

Financial/nonfinancial disclosures: The author has reported to *CHEST* the following conflicts: In the last 3 years Dr Marik has received an honorarium from Pulsion Medical, manufacturer of the PiCCO hemodynamic device, for a lecture delivered at an International Critical Care Symposium and an honorarium from Cheetah Medical, manufacturer of the NiCOM hemodynamic device, for a lecture delivered at medical grand rounds.
Other contributions: The author thanks Rinaldo Bellomo, MD, Michael Hooper, MD, and Mark Flemmer, MD, for their thoughtful review of this manuscript.

References

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992;20(6):864-874.
2. Levy MM, Fink MP, Marshall JC, et al; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
3. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013;381(9868):774-775.
4. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851.
5. Vincent JL, Sakr Y, Sprung CL, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34(2):344-353.
6. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med*. 2013;41(5):1167-1174.
7. Whittaker SA, Mikkelsen ME, Gaieski DF, Koshy S, Kean C, Fuchs BD. Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. *Crit Care Med*. 2013;41(4):945-953.
8. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
9. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
10. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med*. 2006;34(1):15-21.
11. Opal SM, Laterre PF, Francois B, et al; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. *JAMA*. 2013;309(11):1154-1162.
12. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.
13. Nau GJ, Richmond JF, Schlesinger A, Jennings EG, Lander ES, Young RA. Human macrophage activation programs induced by bacterial pathogens. *Proc Natl Acad Sci U S A*. 2002;99(3):1503-1508.
14. Leentjens J, Kox M, van der Hoeven JG, Netea MG, Pickkers P. Immunotherapy for the adjunctive treatment of sepsis: from immunosuppression to immunostimulation. Time for a paradigm change? *Am J Respir Crit Care Med*. 2013;187(12):1287-1293.
15. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol*. 2008;8(10):776-787.

16. Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, Kurosawa S, Remick DG. The pathogenesis of sepsis. *Annu Rev Pathol*. 2011;6:19-48.
17. Skrupky LP, Kerby PW, Hotchkiss RS. Advances in the management of sepsis and the understanding of key immunologic defects. *Anesthesiology*. 2011;115(6):1349-1362.
18. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA*. 2011;306(23):2594-2605.
19. Parrish WR, Gallowitsch-Puerta M, Czura CJ, Tracey KJ. Experimental therapeutic strategies for severe sepsis: mediators and mechanisms. *Ann N Y Acad Sci*. 2008;1144:210-236.
20. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345(8):588-595.
21. Lee WL, Slutsky AS. Sepsis and endothelial permeability. *N Engl J Med*. 2010;363(7):689-691.
22. Goldenberg NM, Steinberg BE, Slutsky AS, Lee WL. Broken barriers: a new take on sepsis pathogenesis. *Sci Transl Med*. 2011;3(88):88ps25.
23. London NR, Zhu W, Bozza FA, et al. Targeting Robo4-dependent Slit signaling to survive the cytokine storm in sepsis and influenza. *Sci Transl Med*. 2010;2(23):23ra19.
24. Zhou F, Peng Z, Murugan R, Kellum JA. Blood purification and mortality in sepsis: a meta-analysis of randomized trials. *Crit Care Med*. 2013;41(9):2209-2220.
25. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. *Crit Care Med*. 2010;38(2):668-678.
26. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med*. 2010;38(4):1045-1053.
27. Westphal GA, Koenig A, Caldeira Filho M, et al. Reduced mortality after the implementation of a protocol for the early detection of severe sepsis. *J Crit Care*. 2011;26(1):76-81.
28. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
29. Kollef MH, Napolitano LM, Solomkin JS, et al. Health care-associated infection (HAI): a critical appraisal of the emerging threat-proceedings of the HAI Summit. *Clin Infect Dis*. 2008;47(suppl 2):S55-S99.
30. Ferrer R, Artigas A, Suarez D, et al; Edusepsis Study Group. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. *Am J Respir Crit Care Med*. 2009;180(9):861-866.
31. Dickinson JD, Kollef MH. Early and adequate antibiotic therapy in the treatment of severe sepsis and septic shock. *Curr Infect Dis Rep*. 2011;13(5):399-405.
32. Joung MK, Lee JA, Moon SY, et al. Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. *Crit Care*. 2011;15(2):R79.
33. Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):420-432.
34. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med*. 2010;36(4):612-620.
35. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med*. 2001;161(15):1837-1842.
36. Marik PE, Lipman J, Kobilski S, Scribante J. A prospective randomized study comparing once- versus twice-daily amikacin dosing in critically ill adult and paediatric patients. *J Antimicrob Chemother*. 1991;28(5):753-764.
37. Prins JM, Büller HR, Kuijper EJ, Tange RA, Speelman P. Once versus thrice daily gentamicin in patients with serious infections. *Lancet*. 1993;341(8841):335-339.
38. Kox M, Pickkers P. "Less is more" in critically ill patients: not too intensive. *JAMA Intern Med*. 2013;173(14):1369-1372.
39. Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. *Crit Care*. 2012;16(1):302.
40. Hilton AK, Bellomo R. Totem and taboo: fluids in sepsis. *Crit Care*. 2011;15(3):164.
41. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? *Intensive Care Med*. 2012;38(3):422-428.
42. Monnet X, Chemla D, Osman D, et al. Measuring aortic diameter improves accuracy of esophageal Doppler in assessing fluid responsiveness. *Crit Care Med*. 2007;35(2):477-482.
43. Rehberg S, Yamamoto Y, Sousse L, et al. Selective V(1a) agonism attenuates vascular dysfunction and fluid accumulation in ovine severe sepsis. *Am J Physiol Heart Circ Physiol*. 2012;303(10):H1245-H1254.
44. Scicluna JK, Mansart A, Ross JJ, Reilly CS, Brown NJ, Brookes ZL. Lipopolysaccharide alters vasodilation to atrial natriuretic peptide via nitric oxide and endothelin-1: time-dependent effects. *Eur J Pharmacol*. 2009;621(1-3):67-70.
45. Marik PE, Desai H. Goal directed fluid therapy. *Curr Pharm Des*. 2012;18(38):6215-6224.
46. Ueda S, Nishio K, Akai Y, et al. Prognostic value of increased plasma levels of brain natriuretic peptide in patients with septic shock. *Shock*. 2006;26(2):134-139.
47. Zhang Z, Zhang Z, Xue Y, Xu X, Ni H. Prognostic value of B-type natriuretic peptide (BNP) and its potential role in guiding fluid therapy in critically ill septic patients. *Scand J Trauma Resusc Emerg Med*. 2012;20:86.
48. Bruegger D, Jacob M, Rehm M, et al. Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. *Am J Physiol Heart Circ Physiol*. 2005;289(5):H1993-H1999.
49. Berg S, Golster M, Lisander B. Albumin extravasation and tissue washout of hyaluronan after plasma volume expansion with crystalloid or hypooncotic colloid solutions. *Acta Anaesthesiol Scand*. 2002;46(2):166-172.
50. Bruegger D, Schwartz L, Chappell D, et al. Release of atrial natriuretic peptide precedes shedding of the endothelial glycocalyx equally in patients undergoing on- and off-pump coronary artery bypass surgery. *Basic Res Cardiol*. 2011;106(6):1111-1121.
51. Jacob M, Chappell D. Reappraising Starling: the physiology of the microcirculation. *Curr Opin Crit Care*. 2013;19(4):282-289.
52. Bark BP, Persson J, Grände PO. Importance of the infusion rate for the plasma expanding effect of 5% albumin, 6% HES 130/0.4, 4% gelatin, and 0.9% NaCl in the septic rat. *Crit Care Med*. 2013;41(3):857-866.
53. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. *Chest*. 2002;122(6):2080-2086.
54. Chung FT, Lin SM, Lin SY, Lin HC. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med*. 2008;102(7):956-961.
55. Jozwiak M, Silva S, Persichini R, et al. Extravascular lung water is an independent prognostic factor in patients with acute respiratory distress syndrome. *Crit Care Med*. 2013;41(2):472-480.

56. Brandt S, Regueira T, Bracht H, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. *Crit Care*. 2009;13(6):R186.
57. Rosenberg AL, Dechert RE, Park PK, Bartlett RH; NIH NHLBI ARDS Network. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med*. 2009;24(1):35-46.
58. Alsous F, Khamiees M, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest*. 2000;117(6):1749-1754.
59. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest*. 2009;136(1):102-109.
60. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39(2):259-265.
61. Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Crit Care*. 2013;17(5):R246.
62. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483-2495.
63. Peake SL, Bailey M, Bellomo R, et al; ARISE Investigators, for the Australian and New Zealand Intensive Care Society Clinical Trials Group. Australasian Resuscitation of Sepsis Evaluation (ARISE): a multi-centre, prospective, inception cohort study. *Resuscitation*. 2009;80(7):811-818.
64. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
65. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
66. Funk DJ, Kumar A. If the central venous pressure is [x], call me … maybe. *Crit Care Med*. 2013;41(7):1823-1824.
67. Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care*. 2011;1(1):1.
68. Marik PE. Noninvasive cardiac output monitors: a state-of the-art review. *J Cardiothorac Vasc Anesth*. 2013;27(1):121-134.
69. Chong SW, Peyton PJ. A meta-analysis of the accuracy and precision of the ultrasonic cardiac output monitor (USCOM). *Anaesthesia*. 2012;67(11):1266-1271.
70. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. *Br J Anaesth*. 2014;112(4):617-620.
71. Phillips RA, Smith BE, Madigan VM, et al. Assessment of the clinical utility of an ultrasonic monitor of cardiac output (the USCOM) and agreement with thermodilution measurement. *Crit Care Resusc*. 2010;12(3):209-213.
72. Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest*. 2013;143(2):364-370.
73. Zorko DJ, Choong K, Gilleland J, et al. Urgent ultrasound guided hemodynamic assessments by a pediatric medical emergency team: a pilot study. *PLoS ONE*. 2013;8(6):e66951.
74. Duchateau FX, Gauss T, Burnod A, Ricard-Hibon A, Juvin P, Mantz J. Feasibility of cardiac output estimation by ultrasonic cardiac output monitoring in the prehospital setting. *Eur J Emerg Med*. 2011;18(6):357-359.
75. Thom O, Taylor DM, Wolfe RE, Myles P, Krum H, Wolfe R. Pilot study of the prevalence, outcomes and detection of occult hypoperfusion in trauma patients. *Emerg Med J*. 2010;27(6):470-472.
76. National Institutes of Health Clinical Center. Emergency department management of sepsis patients: a goal-oriented non-invasive sepsis trial. NCT01453270. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2011. http://clinicaltrials.gov/show/NCT01453270. Updated October 23, 2013.
77. National Institutes of Health Clinical Center. Emergency department (ED) flow-directed fluid optimization resuscitation trial (EFFORT). NCT01128413. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2010. http://clinicaltrials.gov/ct2/show/NCT01128413. Updated August 2, 2011.
78. Pottecher T, Calvat S, Dupont H, Durand-Gasselin J, Gerbeaux P; SFAR/SRLF workgroup. Haemodynamic management of severe sepsis: recommendations of the French Intensive Care Societies (SFAR/SRLF) Consensus Conference, 13 October 2005, Paris, France. *Crit Care*. 2006;10(4):311.
79. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566-1572.
80. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. *J Crit Care*. 2011;26(2):175-179.
81. McCluskey SA, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg*. 2013;117(2):412-421.
82. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg*. 2012;255(5):821-829.
83. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
84. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
85. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg*. 2011;112(6):1289-1295.
86. Jacob M, Paul O, Mehringer L, et al. Albumin augmentation improves condition of guinea pig hearts after 4 hr of cold ischemia. *Transplantation*. 2009;87(7):956-965.
87. National Institutes of Health Clinical Center. Volume replacement with albumin in severe sepsis (ALBIOS). NCT00707122. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2008. http://clinicaltrials.gov/ct2/show/NCT00707122. Updated March 1, 2012.
88. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R; SAFE Study Investigators. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med*. 2011;37(1):86-96.
89. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.
90. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386-391.

91. Bellomo R, Giantomasso DD. Noradrenaline and the kidney: friends or foes? *Crit Care*. 2001;5(6):294-298.
92. Lehman LW, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. *Crit Care Med*. 2013;41(1):34-40.
93. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki LM, Pettilä V. Hemodynamic variables related to outcome in septic shock. *Intensive Care Med*. 2005;31(8):1066-1071.
94. National Institutes of Health Clinical Center. Assessment of two levels of arterial pressure on survival in patients with septic shock (SEPSISPAM). NCT01149278. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2010. http://clinicaltrials.gov/ct2/show/NCT01149278. Updated November 2, 2012.
95. Panwar R, Lanyon N, Davies AR, Bailey M, Pilcher D, Bellomo R. Mean perfusion pressure deficit during the initial management of shock—an observational cohort study. *J Crit Care*. 2013;28(5):816-824.
96. Treggiari MM, Romand JA, Burgener D, Suter PM, Aneman A. Effect of increasing norepinephrine dosage on regional blood flow in a porcine model of endotoxin shock. *Crit Care Med*. 2002;30(6):1334-1339.
97. Jhanji S, Stirling S, Patel N, Hinds CJ, Pearse RM. The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. *Crit Care Med*. 2009;37(6):1961-1966.
98. Georger JF, Hamzaoui O, Chaari A, Maizel J, Richard C, Teboul JL. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. *Intensive Care Med*. 2010;36(11):1882-1889.
99. Persichini R, Silva S, Teboul JL, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. *Crit Care Med*. 2012;40(12):3146-3153.
100. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med*. 2011;39(4):689-694.
101. Hamzaoui O, Georger JF, Monnet X, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care*. 2010;14(4):R142.
102. Abid O, Akça S, Haji-Michael P, Vincent JL. Strong vasopressor support may be futile in the intensive care unit patient with multiple organ failure. *Crit Care Med*. 2000;28(4):947-949.
103. Annane D, Vignon P, Renault A, et al; CATS Study Group. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676-684.
104. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J; CAT Study investigators. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12):2226-2234.
105. Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Leiby B, Marik PE. Norepinephrine or dopamine for septic shock: systematic review of randomized clinical trials. *J Intensive Care Med*. 2012;27(3):172-178.
106. De Baker D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. *Crit Care Med*. 2012;40(3):725-730.
107. Malay MB, Ashton JL, Dahl K, et al. Heterogeneity of the vasoconstrictor effect of vasopressin in septic shock. *Crit Care Med*. 2004;32(6):1327-1331.
108. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med*. 2008;36(6):1701-1706.
109. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med*. 1984;100(4):483-490.
110. Jellema WT, Groeneveld AB, Wesseling KH, Thijs LG, Westerhof N, van Lieshout JJ. Heterogeneity and prediction of hemodynamic responses to dobutamine in patients with septic shock. *Crit Care Med*. 2006;34(9):2392-2398.
111. Bouferrache K, Amiel JB, Chimot L, et al. Initial resuscitation guided by the Surviving Sepsis Campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients: a pilot study. *Crit Care Med*. 2012;40(10):2821-2827.
112. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1997;95(5):1122-1125.
113. Morelli A, Ertmer C, Lange M, et al. Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. *Br J Anaesth*. 2008;100(4):494-503.
114. Morelli A, Ertmer C, Rehberg S, et al. Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. *Crit Care*. 2009;13(4):R130.
115. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.
116. Smith B, Phillips R, Madigan V, West M. Decreased mortality, morbidity and emergency transport in septic shock: a new protocol based on advanced noninvasive haemodynamics and early antibiotics [abstract]. *Crit Care Med*. 2012;40(12)(suppl):A1023.
117. Rissmiller R. Patients are not airplanes and doctors are not pilots. *Crit Care Med*. 2006;34(11):2869.
118. da Silva Ramos FJ, Azevedo LC. Hemodynamic and perfusion end points for volemic resuscitation in sepsis. *Shock*. 2010;34(suppl 1):34-39.
119. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134(1):172-178.
120. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774-1781.
121. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest*. 1993;103(3):900-906.
122. Liu NK, Zhang YP, Titsworth WL, et al. A novel role of phospholipase A2 in mediating spinal cord secondary injury. *Ann Neurol*. 2006;59(4):606-619.
123. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. *Ann Emerg Med*. 2010;55(1):40-46.
124. Nee PA, Rivers EP. The end of the line for the Surviving Sepsis Campaign, but not for early goal-directed therapy. *Emerg Med J*. 2011;28(1):3-4.
125. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow and function during recovery from experimental septic acute kidney injury. *Intensive Care Med*. 2007;33(9):1614-1618.
126. Langenberg C, Wan L, Egi M, May CN, Bellomo R. Renal blood flow in experimental septic acute renal failure. *Kidney Int*. 2006;69(11):1996-2002.

127. Wan L, Bagshaw SM, Langenberg C, Saotome T, May C, Bellomo R. Pathophysiology of septic acute kidney injury: what do we really know? *Crit Care Med*. 2008;36(suppl 4): S198-S203.
128. Huang DT, Angus DC, Barnato A, et al; ProCESS/ARISE/ ProMISe Methodology Writing Committee. Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe. *Intensive Care Med*. 2013;39(10): 1760-1775.
129. Marik PE. Surviving sepsis: going beyond the guidelines. *Ann Intensive Care*. 2011;1(1):17.
130. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182(6): 752-761.
131. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
132. Hotchkiss RS, Karl IE. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *JAMA*. 1992; 267(11):1503-1510.
133. James JH, Luchette FA, McCarter FD, Fischer JE. Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. *Lancet*. 1999;354(9177):505-508.
134. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. *Lancet*. 2005;365(9462):871-875.
135. Marik PE, Bellomo R. Lactate clearance as a target of therapy in sepsis: a flawed paradigm. *OA Critical Care*. 2013; 1(1):3.
136. Garcia-Alvarez M, Marik PE, Bellomo R. Stress hyperlactataemia: present understanding and controversy. *Lancet Diabetes Endocrinol*. 2014;2(4):339-347.
137. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993;269(23): 3024-3029.
138. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med*. 1994;330(24): 1717-1722.
139. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025-1032.
140. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA*. 2013;310(16):1683-1691.
141. Larsen R, Gozzelino R, Jeney V, et al. A central role for free heme in the pathogenesis of severe sepsis. *Sci Transl Med*. 2010;2(51):51ra71.
142. Janz DR, Bastarache JA, Peterson JF, et al. Association between cell-free hemoglobin, acetaminophen, and mortality in patients with sepsis: an observational study. *Crit Care Med*. 2013;41(3):784-790.
143. Fuller BM, Gajera M, Schorr C, et al. The impact of packed red blood cell transfusion on clinical outcomes in patients with septic shock treated with early goal directed therapy. *Indian J Crit Care Med*. 2010;14(4):165-169.
144. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med*. 2008;36(9):2667-2674.
145. Shander A, Fink A, Javidroozi M, et al; International Consensus Conference on Transfusion Outcomes Group. Appropriateness of allogenic red blood cell transfusion; the International Consensus Conference on Transfusion Outcomes. *Transfus Med Rev*. 2011; 25(3):232-246.
146. Marik PE. Glucocorticoids in sepsis: dissecting facts from fiction. *Crit Care*. 2011;15(3):158.
147. Marik PE, Pastores SM, Annane D, et al; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949.
148. Annane D, Bellissant E, Sebille V, et al. Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. *Br J Clin Pharmacol*. 1998;46(6):589-597.
149. Chappell D, Jacob M, Hofmann-Kiefer K, et al. Hydrocortisone preserves the vascular barrier by protecting the endothelial glycocalyx. *Anesthesiology*. 2007;107(5):776-784.
150. Park HY, Suh GY, Song JU, et al. Early initiation of low-dose corticosteroid therapy in the management of septic shock: a retrospective observational study. *Crit Care*. 2012;16(1):R3.
151. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
152. Marik PE, Flemmer MC. The immune response to surgery and trauma: implications for treatment. *J Trauma Acute Care Surg*. 2012;73(4):801-808.
153. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301(22):2362-2375.
154. Torgersen C, Luckner G, Schröder DC, et al. Concomitant arginine-vasopressin and hydrocortisone therapy in severe septic shock: association with mortality. *Intensive Care Med*. 2011;37(9):1432-1437.
155. Russell JA, Walley KR, Gordon AC, et al; Dieter Ayers for the Vasopressin and Septic Shock Trial Investigators. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med*. 2009;37(3):811-818.
156. Bauer SR, Lam SW, Cha SS, Oyen LJ. Effect of corticosteroids on arginine vasopressin-containing vasopressor therapy for septic shock: a case control study. *J Crit Care*. 2008; 23(4):500-506.
157. National Institutes of Health Clinical Center. Adjunctive corticosteroid treatment in critically ill patients with septic shock (ADRENAL). NCT01448109. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2011. http://clinicaltrials.gov/ct2/show/NCT01448109. Updated June 18, 2013.
158. National Institutes of Health Clinical Center. Activated protein C and corticosteroids for human septic shock (APROCCHS). NCT00625209. ClinicalTrials.gov. Bethesda, MD: National Institutes of Health; 2008. http://clinicaltrials.gov/ct2/show/NCT00625209. Updated May 21, 2012.
159. Boyer A, Vargas F, Coste F, et al. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med*. 2009;35(5):847-853.
160. Bufalari A, Giustozzi G, Moggi L. Postoperative intraabdominal abscesses: percutaneous versus surgical treatment. *Acta Chir Belg*. 1996;96(5):197-200.
161. Mermel LA, Farr BM, Sherertz RJ, et al; Infectious Diseases Society of America; American College of Critical Care Medicine; Society for Healthcare Epidemiology of America. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis*. 2001;32(9):1249-1272.