Sepsis and Septic Shock Strategies

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KEYWORDS

- Sepsis • Septic shock • Resuscitation • Goal-directed therapy • Critical care

KEY POINTS

- Three therapeutic principles most substantially improve organ dysfunction and survival in sepsis: (1) early, appropriate antimicrobial therapy; (2) restoration of adequate cellular perfusion; and (3) timely source control.
- The new definitions of sepsis and septic shock reflect the inadequate sensitivity, specify, and lack of prognostication of systemic inflammatory response syndrome criteria. Sequential (sepsis-related) organ failure assessment more effectively prognosticates in sepsis and critical illness.
- Inadequate cellular perfusion accelerates injury and reestablishing perfusion limits injury. The best methods to assess perfusion, target therapy, and reestablish adequate perfusion remain controversial.
- Multiple organ systems are affected by sepsis and septic shock and an evidence-based multipronged approach to systems-based therapy in critical illness results in improve outcomes.

INTRODUCTION

Sepsis and septic shock are syndromes of immense clinical importance. Suspected sepsis accounts for more than half a million emergency department visits annually in the United States.[1] Between 2003 and 2007, there was a 71% increase in the number of hospitalizations for sepsis and a 57% increase in hospital costs.[2] In 2013, sepsis was the most expensive reason for hospitalization, accounting for more than $23.7 billion (6.2%) of total US hospital costs and was the second most common reason for hospitalization, accounting for 3.6% of stays.[3] Of those admitted, 50% are treated in the intensive care unit (ICU) representing 10% of all ICU admissions. Surgical patients in particular account for nearly one-third of sepsis cases in the United States.[4] The mortality of sepsis has been reported to be declining from 45% in 1993 to 37% in

2003, 29% in 2007, and to as low as 18.4% in 2012.[2,5,6] Despite this trend, in another recent examination of 2 large complementary hospital cohorts from 2010 to 2012, sepsis was found to have a mortality range of 34% to 56% and most of those patients were identified to have sepsis at admission.[7] These data emphasize that sepsis mortality remains significant. Although there has been a vast amount of research directed toward improving outcomes in sepsis, 3 therapeutic principles most substantially improve organ dysfunction and survival in sepsis: (1) early, appropriate antimicrobial therapy; (2) restoration of adequate cellular perfusion; and (3) timely source control. Thus, survival is dependent on early recognition and rapid treatment. In the article to follow, the authors summarize recent changes in defining sepsis, highlight pathophysiologic rationale for current therapeutic strategies, and discuss therapeutic approaches to improve outcome.

DEFINITIONS

For more than 2 decades, sepsis had been defined by a combination of the systemic inflammatory response syndrome (SIRS) and the presence of infection (Fig. 1).[8,9] The inadequate sensitivity and specificity of SIRS combined with the latest information regarding sepsis pathobiology prompted a recent revised data-driven definition of sepsis and septic shock: the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (Fig. 2).[10] Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in the total Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection.[11–13] The term "severe sepsis" was removed from the definitions and deemed redundant. Septic shock is a subset of sepsis in which underlying circulatory,
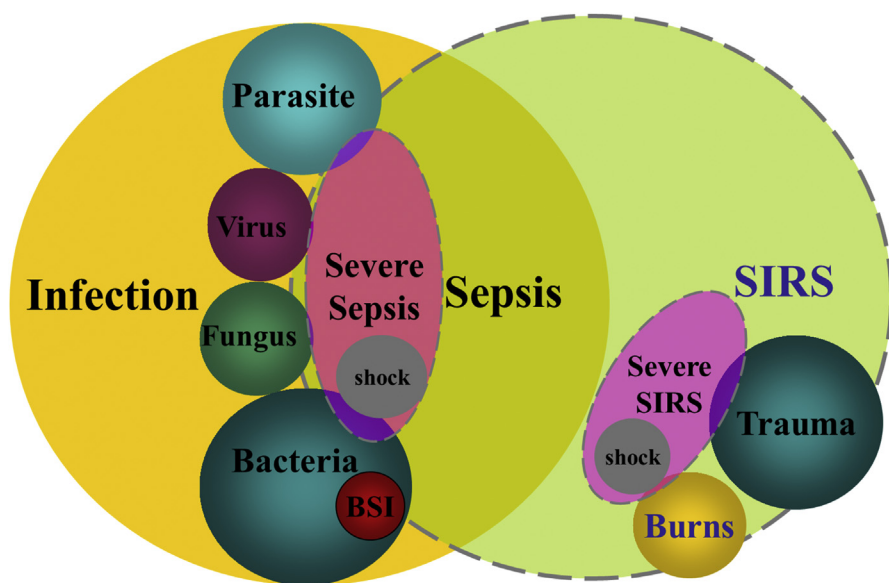
Fig. 1. Early conceptual view of the definition of SIRS, sepsis, severe sepsis, and septic shock whereby infection induces an inflammatory SIRS response. BSI, Blood Stream Infection. (*Adapted from* Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1645; with permission.)
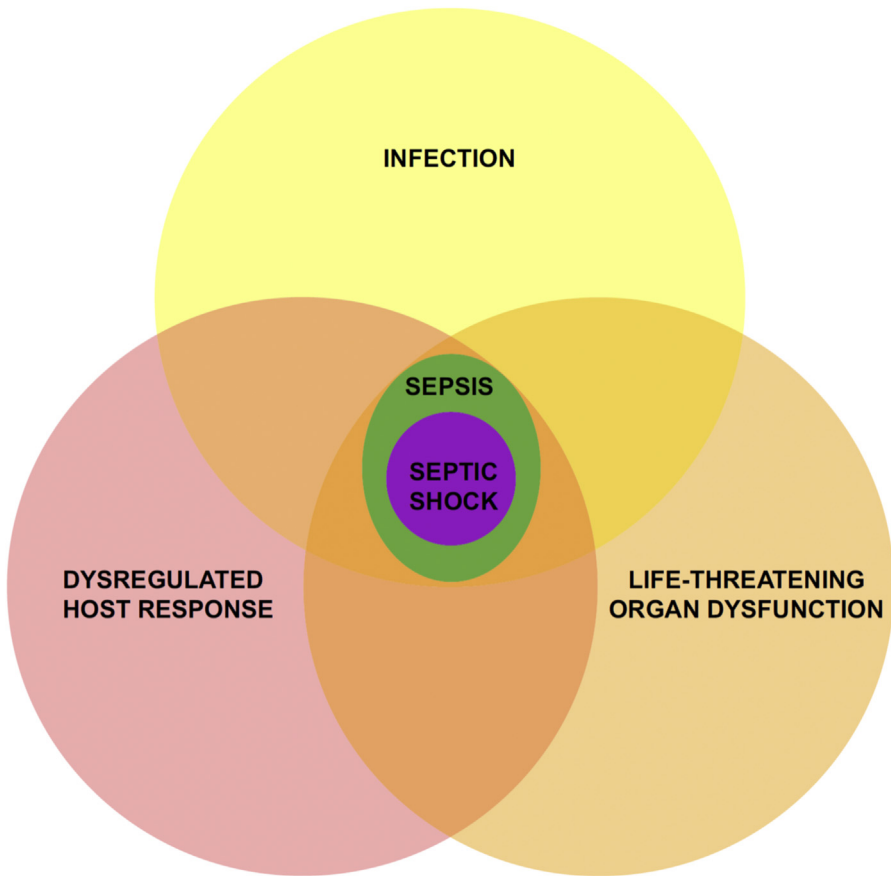
Fig. 2. In Sepsis-3, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and the term "severe sepsis" has been removed. (*From* Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev 2016;274:332; with permission.)

cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. Septic shock in adults can be identified using clinical criteria of hypotension requiring vasopressor therapy to maintain a mean blood pressure of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L, after adequate fluid resuscitation.[14]

The chronologic assessment of organ dysfunction using SOFA has shown to be useful in the prognostication of critically ill patients.[15] SIRS does not prognosticate well in severe sepsis.[16] SIRS criteria has been argued to be overly sensitive and not sufficiently specific, increasing the number of patients diagnosed with sepsis over the years but capturing a larger but less severely ill group of patients.[4,17] In particular, fever and leukocytosis are frequently not present in patients who prove to be infected with organ dysfunction.[18] The SIRS model also implied that sepsis followed a linear trajectory from SIRS to severe sepsis and then septic shock, when in fact it often does not. It has been reported that 68% to 93% of patients admitted to the ICU will meet SIRS criteria[19–21] and that almost half of patients

hospitalized in regular wards will meet SIRS criteria at some time during their stay.[22] Using SOFA, the recently revised definitions are aimed to facilitate earlier recognition and more timely management of patients with sepsis, or at risk of developing sepsis, and identifying those with higher prognostic probability of mortality or poor outcome.

PATHOPHYSIOLOGY

Sepsis is an incompletely understood, nonlinear pathophysiologic process involving the activation and dysregulation of proinflammatory and anti-inflammatory responses of the innate immune system, complement and coagulation systems, metabolic changes, hormonal alterations, mitochondrial dysfunction (cytopathic hypoxia), and epithelial and microcirculatory dysfunction.[23–31] Although each of these systems may be characterized as adaptive, their dysregulated activation creates self-reinforcing organ injury through a final common pathway of profound oxidative cellular stress.[32] Although in sepsis, bacterial products initiate this series of events, shock-induced hypoperfusion and cellular hypoxia and products released by host cell injury accelerate the cascade. The resulting degree of cellular dysfunction demonstrates a nonlinear relationship, increasing exponentially as time progresses. This nonlinear aspect to increasing cellular injury and dysfunction provide a physiologic rationale for the importance of early antibiotic therapy, restoration of cellular perfusion, and source control in sepsis.

Process Initiation

Infection results in activation of the innate immune system. Early activation of the innate immune response occurs by interaction of pattern recognition receptors (predominately a group called toll-like receptors) on the cell surface of tissue macrophages, leukocytes, and endothelium with various microbial products. This interaction results in the activation of transcription factors such as nuclear factor (NF)-κβ that regulate the production of numerous cytokines, chemokines, acute phase proteins, adhesion molecules, receptors, and enzymes involved in the host immune response.[24,26,29] Once activated, the innate immune cells kill bacteria through numerous oxidative pathways.

Propagation to Sepsis

Most commonly, the immune response successfully controls infectious insults without a progression to systemic process. However, at times, the magnitude of the infectious insult produces a much more profound systemic activation. As the magnitude increases, activation of nitric oxide synthase leads to excessive nitric oxide production, increasing oxidative stress, loss of vascular resistance, and resulting distributive shock. Hypoxia, hypoperfusion, and oxidative stress results in the proteolytic cleavage of xanthine dehydrogenase (involved in ATP handling through purine metabolism) to xanthine oxidase. Although xanthine dehydrogenase catalyzes the conversion of hypoxanthine to xanthine and the production of nicotinamide adenine dinucleotide (NADH), xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine with the production of the oxidative species superoxide. Excess superoxide and nitric oxide interact to form other potent oxidative species, such as peroxynitrite that directly injure cellular structures such as DNA, mitochondrial cytochromes, signaling proteins, and cellular and mitochondrial membranes. Oxidative injury of mitochondria further accelerates the process, limiting the ability to use oxygen by the cytochrome system to generate ATP (Fig. 3).[31,32]
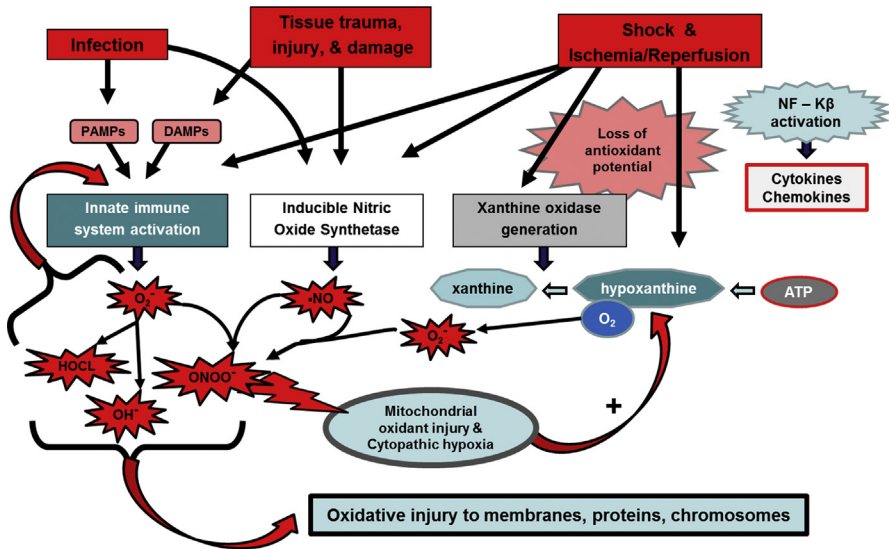
Fig. 3. A simplified model of oxidant stress in sepsis that leads to organ dysfunction. DAMPs, danger-associated molecular patterns; HOCl, hydrochlorous acid; NF-Kβ, nuclear factor; NO, nitric oxide; O_2-, superoxide anion; OH−, hydroxyl anion; ONOO−, peroxynitrite; PAMPs, pathogen-associated molecular patterns.

Organ Dysfunction and Sepsis

The cellular alterations produced by sepsis results in numerous alterations to the host's normal homeostasis, including immune dysregulation; metabolic changes; hormonal alterations; coagulation activation; and mitochondrial, epithelial, and micro-vascular dysfunction.[23–31] The cumulative effects of dysregulation and cellular injury produce significant organ dysfunction, including central nervous system injury (delirium), lung injury (acute respiratory distress syndrome), cardiovascular dysfunction, acute kidney injury, ileus, and hepatic dysfunction.

DIAGNOSIS

There is no gold standard diagnostic tool in sepsis. The early manifestations of sepsis are not specific or particularly sensitive. However, to limit organ dysfunction and reduce mortality, early recognition is paramount. In patients at risk, a high index of suspicion should be maintained. In patients suspected of possible infection and sepsis, a detailed history, physical examination, appropriate imaging, and laboratory data are all important in establishing the presence of sepsis and its source. There is a fairly strong association between declining organ function and the presence of and outcome from sepsis in patients at risk. This association led to the definition in Sepsis-3 of a change in SOFA score ≥2 from baseline in a patient with infection is used to define and diagnose sepsis (**Table 1**). This has been further evaluated and associated with an in-hospital mortality greater than 10% with a predictive value that appears best for patients in the ICU.[13,33]

Sepsis-3 also introduced and validated the concept of the quick SOFA (qSOFA) score as an alert that a non-ICU patient may be deteriorating and may require ICU admission or further workup for sepsis. The Sepsis-3 investigators emphasized

Table 1
Sequential (Sepsis-Related) Organ Function Assessment (SOFA) score

System/Score	0	1	2	3	4
Respiration: Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation: Platelets × $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver: Bilirubin, mg/dL ($\mu mol/L$)	<1.2 (20)	<1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1, or norepinephrine ≤0.1	Dopamine >15 or epinephrine. >0.1, or norepinephrine >0.1
Central nervous system: Glasgow coma scale score	15	13–14	10–12	6–9	<6
Renal: Creatinine mg/dL ($\mu mol/L$); Urine output, mL/d	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440); <500	>5.0 (440): <200

[b] Vasoactive agents are given for at least 1 h and units are μ/kg min.

From Vincent JL, Moreno R, Takala J, et al. Working group on sepsis-related problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22(7):708; with permission.

that although qSOFA is not part of the definition of sepsis, it is a simple scoring system that can be done at the bedside in the ward or emergency department without requiring laboratory data, to identify patients who are at risk of developing a poor outcome (death or ICU stay ≥3 days), and who may benefit from more frequent observations, targeted interventions, or transfer to higher levels of care (**Fig. 4**).[10,34] Recent studies have confirmed that using qSOFA outside the ICU has near equivalent[35,36] or greater[37] prognostic accuracy for in-hospital mortality than SIRS or severe sepsis, but another recent study determined that early warning scores (National Early Warning Score [NEWS] and Modified Early Warning Score) perform even more accurately than qSOFA or SIRS.[38] The NEWS is the mandated tool to identify patients outside the ICU at high risk of clinical deterioration in the United Kingdom.[39–42] The early warning scores, like SIRS, have been partly criticized for being overly sensitive[43,44] and qSOFA has been partly criticized for being too specific and not being sensitive enough, possibly capturing patients too late into their clinical decline.[45–47]

In summary, without a gold standard diagnostic tool for sepsis, our recommendation is to foremost, use a high index of suspicion in patients at risk and clinical judgment to recognize infection, early organ dysfunction, and clinical deterioration. Patients with new organ system dysfunction who are at risk should undergo rapid evaluation and if sepsis is confirmed, early appropriate antimicrobial therapy, resuscitation, and source control as achieving these 3 goals is associated with improved outcomes.[48–50]
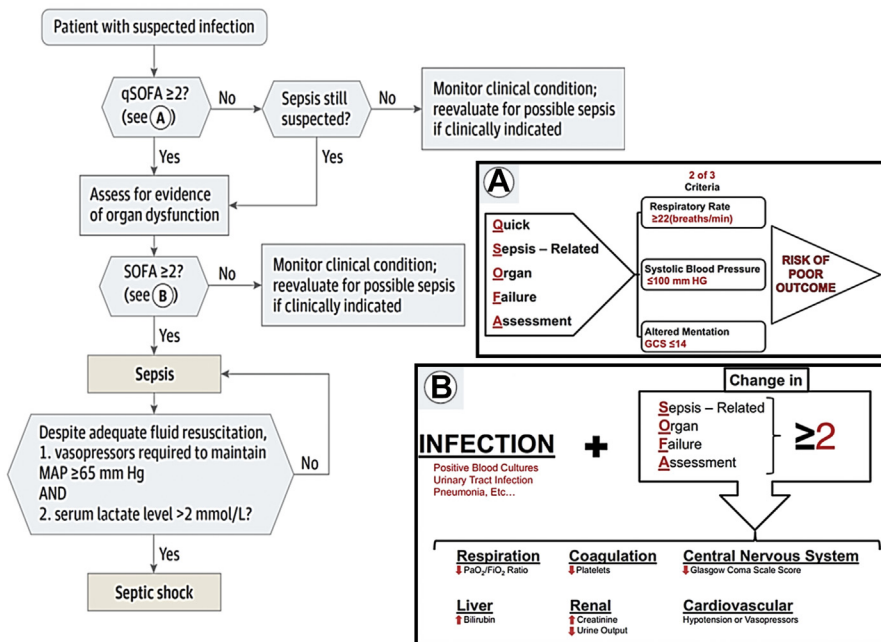
Fig. 4. Identification of patients with sepsis and septic shock using qSOFA and SOFA. (*Adapted from* Singer, Deutschman CS, Seymor CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):808; and Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev 2016; 274:332; with permission.)

INITIAL MANAGEMENT: SOURCE CONTROL AND ANTIBIOTIC THERAPY

All discussions of sepsis would be remiss without mentioning the critical concepts of source control and antibiotic therapy, possibly the 2 most important pillars in the treatment of sepsis. The literature is replete with publications about both topics, and representative literature is discussed here.

We recommend early and aggressive source control to remove the infectious nidus and prevent further progression of organ dysfunction. It may be intuitive to most surgeons that the early control of infectious source results in a strong positive impact on patient outcomes. However, data clearly quantifying the impact are somewhat complex. The 2 most common clinical settings in which surgeons are involved in source control are in the treatment of peritonitis and soft tissue infections. A detailed discussion regarding the approach to source control is beyond the scope of this review, although we will discuss the issue of timing. In one prospective study examining the timing to source control in patients with peritonitis and septic shock, Azuhata and colleagues[51] demonstrated that time to initiation of surgery was an independent predictor of survival by multiple logistic regression analysis. In their study cohort, those who had abdominal source control within 2 hours had a 98% 60-day survival, whereas there were no survivors in the group that waited more than 6 hours for initiation of surgery. For source control in necrotizing soft tissue infections, delay in debridement of more than 24 hours has clear deleterious effects on mortality.[52–54]

The second critical pillar in the treatment of sepsis is antibiotic treatment, and both the timing and appropriateness of antibiotic therapy. We recommend that antibiotic agents targeting the most likely pathogens suspected should be initiated as soon as the diagnosis of sepsis and septic shock is reasonably certain. Appropriate cultures should be obtained before antimicrobial therapy is initiated as long as obtaining said cultures does not delay starting the antimicrobials, this should include 2 sets of blood cultures.[55,56] Appropriate cultures before antimicrobial therapy is associated with improved outcomes.[57,58] Although the influence of timing and appropriateness of antibiotic therapy may be altered by other factors, such as the severity of disease and timing and appropriateness of source control, there is a huge body of literature supporting the critical role of this pillar. The influence of timing of antibiotic treatment in patients with severe sepsis and septic shock on outcome was investigated by Ferrer and colleagues[59] in retrospective analysis of 28,150 patients in the Surviving Sepsis Campaign's database. The adjusted in-hospital mortality odds ratio increased significantly with every hour that antibiotic treatment was delayed after 2 hours from when screening criteria were fulfilled, increasing to an odds ratio of 1.52 at 6 hours. Their findings are consistent with numerous other studies of patients with sepsis and shock.[49,60–63] However, as the time window for the introduction of therapy is compressed and variability of patient populations and severity of illness increases in studies, the significance of early antibiotic therapy is more difficult to establish. In a meta-analysis of studies examining 2 separate time windows for therapy, either (1) less than or greater than 3 hours from triage in the emergency department and/or (2) less than or greater than 1 hour from recognition of severe sepsis/septic shock, odds ratios favored earlier therapy, but both confidence intervals crossed 1.[64]

Appropriate empiric coverage of the pathogens involved is also of significant importance. Many studies have demonstrated roughly a 50% reduction in mortality with appropriate versus inappropriate empiric antibiotics.[65–73] In a retrospective analysis of more than 5700 patients admitted to 22 different institutions with septic shock, Kumar and colleagues[68] showed a fivefold increase in hospital mortality for those

patients who had inappropriate antibiotic therapy. Thus, an understanding of the most likely pathogens involved in the clinical infection, local sensitivity patterns for likely pathogens, and the presence of various risk factors for the involvement of resistant bacteria is of significant importance if one is to achieve appropriate empiric therapeutic coverage. Risk factors for resistance include antibiotic exposure and acquisition of infection within a health care setting. For example, in gram-negative sepsis, recent antibiotic exposure was associated with a hospital mortality of 51% compared with 34% in those patients who had no recent exposure.[74] In a study of hospital-acquired intra-abdominal infections, 3 agents were required to adequately empirically cover most pathogens and inadequate coverage was an independent predictor of mortality.[71]

Although appropriate and timely antibiotic therapy likely substantially improves outcome in patients with sepsis and septic shock, unnecessary antibiotic exposure contributes to the risk of subsequent antibiotic-resistant infections, may actually increase the risk of all subsequent infectious complications, and likely increases the risk of adverse events due to antibiotics.[67,75–87] Two strategies, in particular, have been advocated to limit unnecessary antibiotic exposure: (1) de-escalation and (2) limiting treatment duration to what can be supported by literature. Broad empiric antibiotic therapy is required in many settings to adequately cover most likely pathogens. Thus, with appropriate culture data, including bacterial species identification and sensitivities, some agents may prove to be unnecessary. To limit antibiotic exposure and its added risk of the development of resistance, de-escalation of therapy is advocated. However, limited data exist to support enhanced clinical outcome for the specific infectious event.[88]

Limiting antibiotic duration to a period that is supported by prospective data also limits unnecessary antibiotic therapy. Until relatively recently, the duration of antibiotic therapy has been driven by empiric observations and an assumed requirement for resolution of inflammatory symptoms and not prospective data. However, good prospective randomized data now exist for both intra-abdominal infection and pneumonia. In both settings, shorter durations of antibiotic therapy have shown to be equivalent to longer courses in multiple disease processes. In the randomized Study to Optimize Peritoneal Infection Therapy (STOP-IT) trial for intra-abdominal infections, 4 days of therapy after source control was equivalent to any longer courses based on resolution of clinical signs of inflammation.[89] Similarly, 8 days of treatment for ventilator-associated pneumonia was equivalent to longer courses of therapy.[86] Persistence of organ dysfunction and signs of infection in the setting of adequate antibiotic therapy should prompt an evaluation of adequate source control or a change in pathogens rather than simply extending therapy.[90,91]

INITIAL MANAGEMENT: RESUSCITATION

The Surviving Sepsis Campaign (SSC) guidelines were first published in 2004, with revisions in 2008 and 2012.[92–96] In March 2017, the fourth revision of the SSC guidelines were published jointly in *Critical Care Medicine* and *Intensive Care Medicine*.[97,98] The updated guideline included 55 international experts representing 25 international organizations involved in the care of sepsis and provides 93 recommendations overall and 18 "best practice recommendations" on the early management of sepsis and septic shock incorporating literature searches through July 2016. Compliance with the implementation of previous iterations of the SSC guidelines and resuscitation bundles into clinical practice have been associated with decreased mortality that is sustained and improves with the time of compliance.[50,99,100] Many of the management

strategies discussed in this article are based on these evidence-based consensus guidelines.

Sepsis and septic shock are considered medical emergencies, and initial resuscitation of a patient should occur immediately.[97,98] The landmark study by Rivers and colleagues[48] showed that more rapidly achieving targeted endpoints of resuscitation during the first 6 hours of resuscitation of patients with severe sepsis and septic shock was associated with improved outcome. It is currently recommended that initial resuscitation from sepsis-induced hypoperfusion includes at least 30 mL/kg of intravenous crystalloid fluid given within the first 3 hours (**Fig. 5**),[97,98,101,102] which is associated in the literature with good outcomes as shown in the ARISE, ProCESS, and ProMISe trials.[103–105] Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status and evaluation of fluid responsiveness. One of the most significant changes to the new SSC guidelines include recommending the use of dynamic (eg, sequential bedside echocardiography and vena cava ultrasound, pulse or stroke volume variations induced by mechanical ventilation or passive leg raise test) over static variables (intravascular pressures or volumes, such as central venous pressure) to predict volume responsiveness. Central venous pressure (CVP) has been shown in a multiple studies to be a good indicator of preload but to not predict fluid responsiveness.[106–108]

Monnet and colleagues[109] recently published an excellent review for the prediction of fluid responsiveness that includes dynamic variables. A clinician's armamentarium
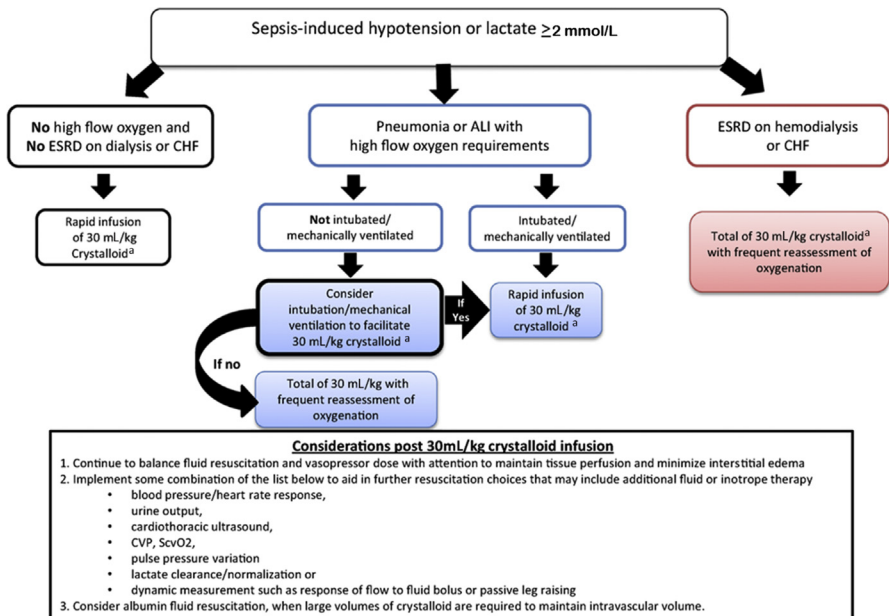
Fig. 5. A proposed application of fluid resuscitation in adult septic shock involving administration of 30 mL/kg of intravenous crystalloid for sepsis-induced hypotension with examples of reassessment tools to assess fluid responsiveness, following that initial fluid infusion. [a] Administer 30 mL/kg crystalloid within first 3 hours. ALI, acute lung injury; CHF, congestive heart failure; CVP, central venous pressure; ESRD, end-stage renal disease; ScvO2, superior vena cava oxygen saturation. (*Adapted from* Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med 2017;3:300; with permission.)

for assessing fluid responsiveness can include the following: pulse pressure variations/stroke volume variations (median threshold of 12%),[110–112] inferior vena cava diameter variations (distensibility index threshold of 18%, which discriminates fluid responders and nonresponders with 90% sensitivity and 90% specificity),[113] superior vena cava diameter variations (collapse >36% discriminates fluid responders and nonresponders with 90% sensitivity and 100% specificity),[114] passive leg raising (pooled sensitivity of 85% and specificity of 91% when used to measure cardiac output continuously in real time),[115–117] end-expiratory occlusion test (expiratory hold on the ventilator for at minimum 15 seconds, with threshold for increase in cardiac output >5%),[118] "mini"-fluid challenge of 100 mL of colloid (change in the velocity time integral of the left ventricular outflow tract measured with echocardiography, threshold of 10% increase),[119] and "conventional" fluid challenge of 500 mL of crystalloid.[120,121] Monnet and colleagues[109] emphasize to not hold fluids in cases of clear-cut hypovolemic shock and the early phases of septic shock (when fluid has not yet been administered) if waiting for tests of fluid responsiveness, and that fluid should be administered only when it will increase cardiac output, at all times weighing the risks and benefits of volume overload.

EARLY GOAL-DIRECTED THERAPY VERSUS STANDARD THERAPY

Previous resuscitation goals in the SSC guidelines[92–96] were based on early goal-directed therapy (EGDT), which is derived largely from the results of the previously mentioned pivotal trial by Rivers and colleagues,[48] which showed an absolute reduction in mortality of 16% in patients with severe sepsis and septic shock who received goal-directed therapy over standard therapy. EGDT (Fig. 6) includes identification of high-risk patients, proper cultures, source control, appropriate antibiotics, and early insertion of a central venous catheter to measure central venous oxygen saturation (ScVO$_2$) with therapy titrated to CVP 8 to 12, mean arterial pressure (MAP) $\geq$65 using vasopressors as necessary, urine output $\geq$0.5 mL/kg per hour, and ScVO$_2$ $\geq$70% within the first 6 hours of resuscitation. It also includes using inotropes and transfusing red blood cells (RBCs) (for a goal hematocrit $\geq$30%) to restore oxygen delivery to meet ScVO$_2$ goals. Standard therapy resuscitated to a CVP of 8 to 12 but did not use ScVO$_2$ monitoring.[48] A meta-analyses of randomized control trials by Gu and colleagues[122] showed a significant survival benefit with EGDT in the subgroup that received early intervention within 6 hours.

Despite these data, concerns with strict adherence to EGDT include the external validity of a single-center experience, and costs, risks, resources, compliance, and the complexity of implementation of EGDT-based sepsis bundles.[123–126] With these concerns in mind, more than a decade after Rivers and colleagues[48] and the first version of the SSC guidelines,[92] the ARISE,[103] ProCESS,[104] and ProMISe[105] trials aimed to compare EGDT with standard therapy: they showed equivalent survival between the two. Yet, in all 3 studies, patients had early risk stratification of high-risk patients using SIRS, lactate screening, early antibiotics, and more than 30 mL/kg of intravenous fluid before randomization, and then reported impressively low sepsis mortality rates for all treatment groups compared with multiple previous observational studies.[127] These revelations imply that the standard treatment of sepsis has changed dramatically via the influence of the SSC guidelines,[92–96] the trial by Rivers and colleagues[48] advocating EGDT, and data showing that delay of appropriate antibiotic administration increases mortality,[49,59,68] as sepsis mortality has progressively decreased since the adoption of these landmark publications.[6] Multiple systemic reviews and meta-analyses that include the data from ARISE, ProCESS, and ProMISe

suggest that EGDT still has utility, as it shows no clinical harm, but strict adherence to EGDT may increase vasopressor use and ICU admission, and they suggest that alternative strategies may provide equal reduction in mortality.[97,98,127–132]

It may be inappropriate to entirely abandon EGDT, as there remains evidence for positive outcomes when obtaining certain goal-directed resuscitation endpoints. This warrants a discussion on the evidence for monitoring and optimizing CVP, hemoglobin, $ScVO_2$, lactic acid, and MAP in managing sepsis and septic shock. Knowing these data points can define the hemodynamic phenotype of each patient, which may help optimize and individualize clinical decisions. Recently proposed by Rivers and colleagues,[133] each hemodynamic phenotype, defined by lactic acid level, central
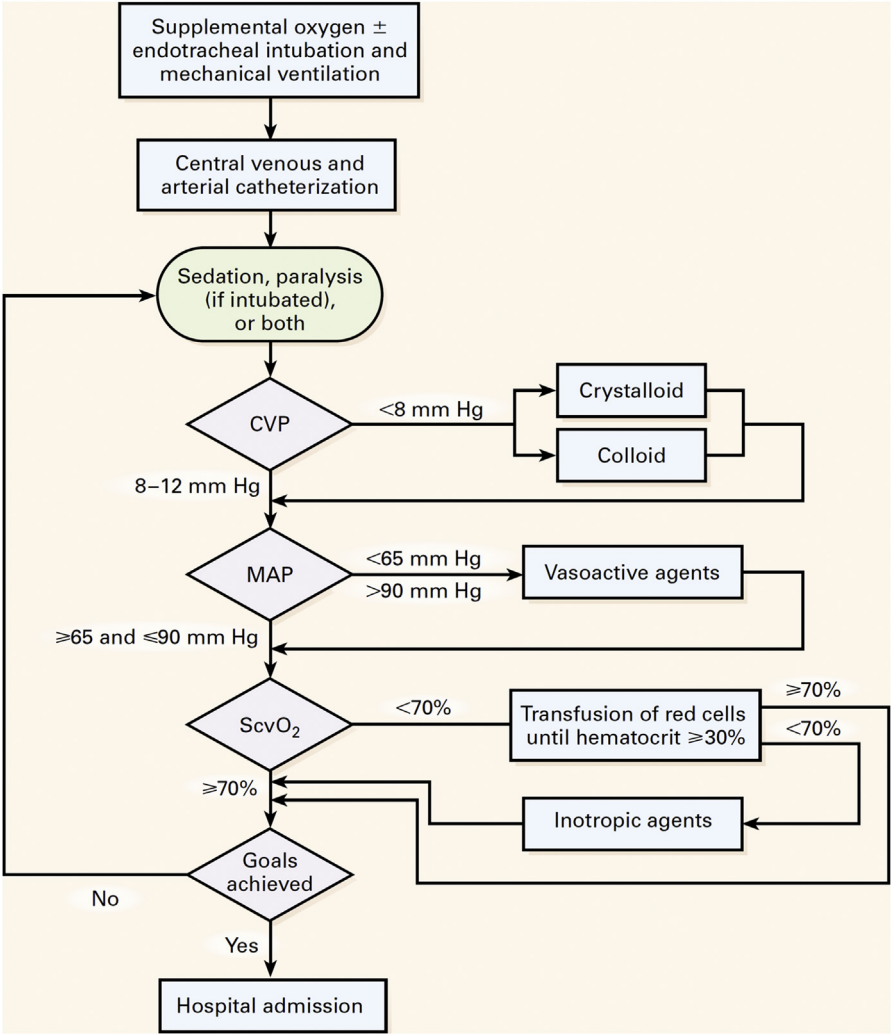

Fig. 6. The classic algorithm for early goal-directed therapy for sepsis. (From Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1371; with permission.)

venous or mixed venous oxygen saturation, and MAP has a predicted, evidence-based mortality that is dependent on the subtypes of hemodynamic derangement and their associated treatment options (Fig. 7).[127]

CENTRAL VENOUS PRESSURE

We recommend that CVP alone, as previously discussed, should not be used to guide fluid responsiveness,[106–108,134,135] but the general use of CVP in the treatment of severe sepsis and septic shock has been associated with improved outcomes and can be considered "essential for the measurement of the volume state, the performance of
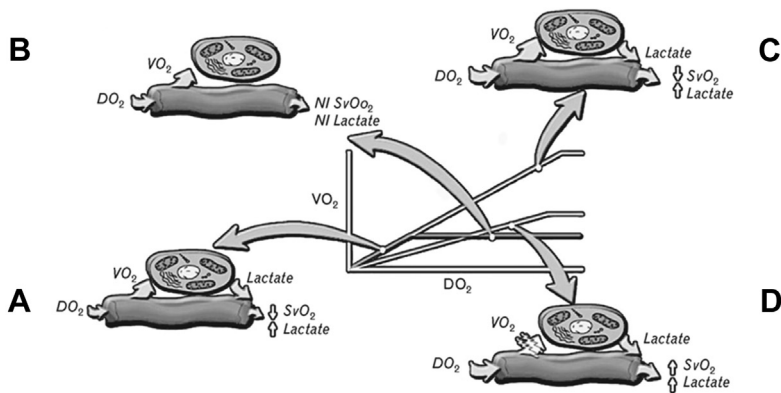
Stage	Haemodynamic Derangements	Lactate	SvO$_2$/ScvO$_2$	MAP	Mortality (%)	Treatment and Comments
A	Hypovolaemia, vasodilatation, myocardial suppression, increased metabolic demands	Normal ↑	↓	↓	15% (142) 23% (165)	Volume, vasopressors, correct anaemia, inotropic therapy, mechanical ventilation
A				Normal	21% (183) 24.9% (184) 35.2% (185) (cryptic shock)	
B	Resuscitated, compensated and vasodilatory	Normal - ↑	Normal	↓	19.0% (183) 20% (186)	Hyperdynamic, vasopressors, low-dose corticosteroids
B				Normal	7.7% (187) 11.8% (188) 21% (143)	
C	Continued DO$_2$ dependency, increased metabolic demands	↑	↓	↓	37.9% (188) 40% (143) 42.9% (187) 48% (184) 51% (142)	Decrease VO$_2$ and further augmentation of DO$_2$
D	Microcirculatory or OER defections and impairment of VO$_2$ Decreased VO$_2$ (dysoxic)	↑	↑	↓	34% (143) 40% (142) 41.7% (188) 52.3% (189) 60.3% (185)	Microcirculatory rescue, source control

Fig. 7. Proposed hemodynamic phenotypes of sepsis and septic shock. DO$_2$, systemic oxygen delivery; OER, oxygen extraction ratio; Vo$_2$, systemic oxygen demands. (From Rivers EP, Yataco AC, Jaehne AK, et al. Oxygen extraction and perfusion markers in severe sepsis and septic shock: diagnostic, therapeutic and outcome implications. Curr Opin Crit Care 2015;21:383; with permission.)

the heart and the systemic vascular resistance."[135–137] CVP can be helpful in identifying a specific type of shock, but we recommend using it in conjunction with other variables. Previous SSC guidelines recommended a CVP goal of 8 to 12 mm Hg.[95,96] The updated guidelines no longer give a CVP goal, and instead recommend using dynamic measures (such as sequential echocardiography) over static variables to assess fluid responsiveness.[97,98]

HEMOGLOBIN

We recommend that hemoglobin levels be optimized and individualized based on patient characteristics and oxygen delivery needs. Elevating hemoglobin levels via transfusion may improve oxygen delivery if cardiac output is unchanged. In the setting of persistent hypoperfusion, previous SSC guidelines aimed for a hematocrit greater than 30% for a goal $ScVO_2$ greater than 70% in the first 6 hours.[95,96] The new SSC recommendation is to perform RBC transfusion for hemoglobin levels less than 7.0 g/dL in adults without myocardial ischemia, severe hypoxemia, or acute hemorrhage.[97,98] This is supported by the Transfusion Requirements in Septic Shock (TRISS) trial, which showed no significant difference in 90-day mortality for a transfusion threshold of 7 g/dL versus 9 g/dL in patients with septic shock admitted to the ICU.[138] At long-term follow-up, the TRISS study population showed no difference in mortality rate or health-related quality of life at 1 year.[139] Additionally, in the ProCESS trial, the EGDT group received RBC transfusion for hemoglobin less than 10 g/dL when $ScVO_2$ was less than 70% after initial resuscitation and the standard therapy group received transfusion for hemoglobin less than 7.5 g/dL, there was no significant difference in 60-day in-hospital mortality and 90-day mortality.[104] Of note, the median low level of hemoglobin in the TRISS trial was 8.5 g/dL, the highest lactate level was approximately 2.5 mmol/L, and lowest SCVO2 was approximately 70% in both the ProCESS and TRISS trials, which may indicate their patients had adequate oxygen delivery at baseline. A recent meta-analysis that included mainly observational studies and one randomized controlled trial (RCT) (the TRISS trial), concluded that restrictive RBC transfusion in sepsis has neither benefit nor harm compared with liberal transfusion strategies.[140]

CENTRAL VENOUS OXYGEN SATURATION

We recommend early and sequential ScVO2 monitoring with a goal of normalization if a central venous catheter is in place. $ScVO_2$ represents the balance between oxygen delivery and oxygen consumption as measured by the venous blood returning to the heart. A low $ScVO_2$ is a common finding in sepsis and has been used in EGDT as a measure of inappropriate tissue oxygenation.[48,95,96] A low $ScVO_2$ may indicate a decrease in oxygen delivery (macrocirculatory failure), an increase in oxygen extraction, or both. An $ScVO_2$ less than 70% on ICU admission is associated with a 10.4% increase in 28-day mortality (37.8% vs 27.4%).[141] If $ScVO_2$ remains less than 70% within the first 6 hours of resuscitation, the mortality rate has been reported to increase by 19% (40% for hypoxia vs 21% in patients with normoxia).[142] Yet even if macrocirculatory flow is optimized in sepsis, microcirculatory (distributive) flow is often disrupted,[30,143–147] and in addition mitochondrial dysfunction (cytopathic hypoxia) also occurs.[31,148–153] In other words, oxygen supply may be prevalent, but the tissue never sees it or the tissue cannot use it adequately, which results in an elevated $ScVO_2$. An $ScVO_2 \geq 90\%$ within the first 6 hours of resuscitation increases mortality rate by 13% (34% for hyperoxia vs 21% for normoxia).[142] In the EGDT trial by Rivers and colleagues,[48] initial ScVO2 was 49%, whereas in ARISE, ProCESS, and ProMISe, it was 72.7%, 71.0%, and 70.1%, respectively.[103–105] This is

another example of the dissimilarity in the initial patient characteristics and level of sickness compared with the trial by Rivers and colleagues. As a result, recent reviews call into question how many patients in ARISE, ProCESS, and ProMISe required actual intervention to optimize their ScVO2.[127,128]

LACTIC ACID

We recommend early and sequential lactic acid monitoring with a goal of lactic acid level normalization. The previous and current SSC guidelines recommend targeting resuscitation to normalize lactate in patients with elevated lactate levels.[95–98] Traditionally, an elevated lactate level in the shock state has been thought to be a marker of tissue hypoperfusion and secondary anaerobic metabolism.[154] Lactate "clearance" was popularized in the study by Nguyen and colleagues[155] in 2004 that showed that patients with severe sepsis and septic shock with a higher percentage decrease in lactate levels after 6 hours of emergency department intervention had improved mortality, and presumed that lactate normalization was a marker for resolution of global tissue hypoxia. Additional studies in 2010 by Jones and colleagues[156] and Jansen and colleagues,[157] followed by a recent meta-analysis of RCTs, confirmed that the use of lactate "clearance" as a goal to guide early resuscitation therapy was associated with a reduction in the risk of death in adults with sepsis.[158]

Hyperlactatemia has been confirmed to be a marker of illness severity, is a strong predictor of mortality in sepsis, and the estimated mortality reduction from lactate screening approaches 11%.[159–165] Yet it is no longer clear that an elevated serum lactate is a direct measure of tissue hypoperfusion. Hyperlactatemia in sepsis also may be an adaptive response to stress explained by increased aerobic glycolysis, which facilitates improved metabolic efficiency through lactic oxidation.[166–168] Regardless of the mechanism of production, evidence suggests that lactate level reduction of at least 10% at a minimum of 2 hours after resuscitation is an appropriate way to evaluate initial response to the resuscitation and that the addition of lactate level normalization to sepsis bundles is associated with improved mortality.[155,156,169]

MEAN ARTERIAL PRESSURE

We agree with the current SSC guidelines that recommend an initial target MAP of 65 mm Hg in patients with septic shock requiring vasopressors, if fluid resuscitation of 30 mL/kg fails to achieve that goal.[97,98] MAP drives global tissue macrocirculatory perfusion and has variable effects on the microcirculation.[170–173] There is ongoing interest in validation of microcirculatory monitoring measures to improve organ perfusion and tissue oxygenation.[174] Prolonged hypotension in the first 6 hours of resuscitation with an MAP less than 65 mm Hg is one of the most powerful predictors of mortality in septic shock and each hour delay in initiating norepinephrine to reach goal MAP is associated with a 5.3% increase in mortality.[175,176] In one retrospective review of 2849 patients with septic shock who survived to 24 hours, Waechter and colleagues[177] concluded that the focus of the first hour of resuscitation should be aggressive fluid administration and to start vasopressors after the first hour, as the lowest mortality rates were when vasopressors were started between 1 and 6 hours after onset of septic shock.

Higher MAP targets also have been studied, including a large randomized clinical trial of 776 patients by Asfar and colleagues[178] that showed no difference in 28-day or 90-day mortality targeting an MAP of 65 to 70 mm Hg versus 80 to 85 mm Hg, but showed significantly increased rates of cardiac arrhythmia in the higher MAP target group. Other studies have shown that titration of norepinephrine to achieve

MAPs from 65 to 85 mm Hg resulted in an increases in cardiac index but did not change urinary output, arterial lactate levels, or oxygen consumption.[171,179] In Asfar and colleagues,[178] a subgroup of patients with chronic hypertension had lower rates of serum creatinine doubling and decreased need for renal replacement therapy when targeting an MAP of 80 to 85 mm Hg. Recent consensus guidelines recommend targeting an MAP higher than 65 mm Hg in septic patients with a history of hypertension "who improve" with higher blood pressure.[134]

SUMMARY: RESUSCITATION STRATEGY

It is clear that early quantitative resuscitation strategies impact a mortality reduction in sepsis and this has been validated in meta-analyses.[122,180] EGDT still has utility, and the benefit is especially evident in populations of septic patients with predicted high mortality (>40%).[181] It is important to understand the utilization and evidence for CVP, hemoglobin, $ScVO_2$, lactic acid, and MAP to optimize patient outcomes in sepsis and septic shock. We advocate a strategy of resuscitation and hemodynamic monitoring that closely align with expert consensus guidelines.[97,98,134] This also should include frequent measurement of heart rate, blood pressure, body temperature, and physical examination, including capillary refill, urine output, and mental status, with liberal use of a central venous catheter, arterial line, and dynamic measures (preferably sequential bedside echocardiography and vena cava ultrasound) over static variables to predict fluid responsiveness, and in complex patients or patients with refractory shock with right ventricular dysfunction: pulmonary artery catheterization.[134] We encourage an awareness of the unique and dynamic hemodynamic phenotype of each patient and recommend individualizing treatment as appropriate (see **Fig. 7**).[133,141,142,164,182–188]

SYSTEMS-BASED THERAPY
Septic Encephalopathy and Delirium

Septic encephalopathy is a transient and reversible brain dysfunction that affects 30% to 70% of patients with septses.[189,190] It results from inflammatory, ischemic, and neurotoxic processes and is characterized by altered mental status that can range from delirium to coma.[191–193] Delirium is a disturbance and change in baseline attention and awareness, and a change in cognition, which develops over a short period and fluctuates.[194] Delirium is associated with increased ICU and hospital stay, increased cost of care, increased mortality, incomplete recovery, and increased rates of cognitive impairment and decline following ICU care.[195–201] The Society of Critical Care Medicine recognizes delirium as a serious public health problem and recommends routine monitoring of delirium in adult ICU patients.[202] The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is a validated and reliable tool to diagnose delirium and is more sensitive than physician assessment. Delirium is defined as a response to verbal stimulation with eye opening (Richmond Agitation-Sedation Scale score −3 to +4) and a positive CAM-ICU.[203,204] Recognizing delirium is the first step toward intervention and may offer insights for possible prevention.

Ultimately, the 3 previously mentioned therapeutic principles that most substantially improve organ dysfunction and survival in sepsis, (1) early, appropriate antimicrobial therapy, (2) restoration of adequate cellular perfusion, and (3) timely source control, still apply to prevent and manage septic encephalopathy and delirium. In addition, we recommend implementation and adherence to an ICU liberation model involving the ABCDEF (Awakening and Breathing Coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family engagement) bundle, which is an

evidence-based guide to improve and renormalize cognitive, emotional, and physical capacity and prevent a disability known as "the post–intensive care syndrome" (Fig. 8).[205,206] In a recent large study, ABCDEF bundle compliance was independently associated with improved survival and more days free of delirium in critically ill patients.[207]

Septic Cardiomyopathy and Inotropic Therapy

Sepsis-induced myocardial dysfunction is common, especially in septic shock, and occurs in 20% to 50% of septic patients overall.[208–211] Adequate fluid resuscitation to restore ventricular filling pressures and adequate MAP (restoration of adequate cellular perfusion), along with early, appropriate antimicrobial therapy and timely source control remain the mainstays of management. The pathophysiology and clinical importance of septic myocardial dysfunction is complex, evolving, and not yet fully elucidated.[212–214] Diastolic dysfunction is more common than systolic dysfunction. Systolic dysfunction does not appear to increase mortality in septic patients and there remains conflicting data on the effects of diastolic dysfunction. Decreases in ejection fraction are reversible, with full recovery usually in 7 to 10 days in survivors.[209,214–219] An elevated troponin level is also common in sepsis, even in the absence of coronary artery disease, and in fact does identify patients at higher risk of death.[220,221]

ICU Liberation: ABCDEF Bundle

Symptoms Pain, Agitation, Delirium Guidelines	Monitoring Tools	Care ABCDEF Bundle	Done
Pain	Critical-Care Pain Observation Tool (CPOT) NRS Numeric Rating Scale BPS Behavioral Pain Scale	A: Assess, Prevent and Manage Pain	☐
Agitation	Richmond Agitation-Sedation Scale (RASS) Sedation-Agitation Scale (SAS)	B: Both Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT) C: Choice of Analgesia and Sedation	☐ ☐
Delirium	Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) Intensive Care Delirium Screening Checklist (ICDSC)	D: Delirium: Assess, Prevent and Manage E: Early Mobility and Exercise F: Family Engagement and Empowerment	☐ ☐ ☐

Fig. 8. ICU liberation model involving the ABCDEF for use as a rounding checklist. (*From* Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. Crit Care Med 2017;45(2):324; with permission.)

A subset of patients may have a complex hemodynamic picture requiring either invasive or noninvasive cardiac output monitoring. Patients with persistently low measured cardiac output despite adequate left ventricular filling pressures (volume resuscitated) may benefit from inotropic therapy if that will also improve oxygen delivery and improve tissue perfusion. The current recommended first-line inotrope is dobutamine and it was the inotrope of choice used in the EGDT studies.[48,97,98,103–105] Yet there remains no randomized clinical trial data to support this recommendation. Raising cardiac output to "supranormal" levels has not been shown to improve outcomes and is not recommended.[222–224]

Atrial Fibrillation

Atrial fibrillation is an independent predictor of mortality in critically ill patients, and we recommend appropriate workup and treatment. In one study, the development of any atrial fibrillation during the first 4 days in the ICU was associated with a 62% increased risk of in-hospital mortality.[225] New-onset atrial fibrillation is a common complication in sepsis, occurring in up to 23% of patients and is also independently associated with poor outcomes (prolonged length of stay and increased mortality). Developing atrial fibrillation during sepsis is associated with a twofold increase in cumulative ICU mortality and a 50% increase in daily risk of death in the ICU.[226,227] Failure to restore a normal sinus rhythm in atrial fibrillation in septic patients may be associated with increased in-hospital mortality.[228] Beta blockers may have beneficial effects in septic patients,[229] and in one study of patients who were septic with atrial fibrillation, intravenous beta blocker treatment was associated with lower mortality as compared with intravenous calcium channel blockers, digoxin, and amiodarone.[230] Patients are commonly anticoagulated for atrial fibrillation to reduce the risk of ischemic stroke. In one study in patients with atrial fibrillation during sepsis, parenteral anticoagulation was associated with higher bleeding rates but not reduced risk of ischemic stroke.[231] Despite the possible applications of these studies, there currently is not enough evidence to recommend an individualized approach to atrial fibrillation in sepsis and septic shock beyond consensus guideline evidence and management.[232–234]

Vasoactive Agents

We recommend norepinephrine as the first-line vasoactive agent in septic shock. There are multiple choices of vasoactive agents to choose from for restoring perfusion pressure in septic shock, including norepinephrine, dopamine, epinephrine, vasopressin, and phenylephrine. Prolonged hypotension and a delay in starting vasopressor therapy is associated with increased mortality, as previously iterated in our discussion on MAP goals. The users' guide to the 2016 SSC guidelines provides an exceptional flow diagram for vasopressor use in adult septic shock (**Fig. 9**).[101,102]

The 2012 and 2016 recommendation from the SSC guidelines is to use norepinephrine as the first-choice vasopressor and to target an MAP of 65 mm Hg.[95–98] Older recommendations were for norepinephrine or dopamine as the first-line agent.[92,93] This recommendation subsequently changed as evidence showed that dopamine was associated with greater or equivocal mortality and a higher incidence of arrhythmias compared with norepinephrine in patients with septic shock.[95–98,235–238] Dopamine has not been shown to provide renal protection.[237] It is currently recommended to use dopamine only in highly selected patients as an alternative to norepinephrine in those with low risk of tachyarrhythmias and absolute or relative bradycardia.[97,98]

A relative vasopressin deficiency may exist in septic shock.[239,240] The Vasopressin and Septic Shock Trial (VASST) showed the addition of low-dose vasopressin to norepinephrine infusion was safe, and suggested it may decrease mortality in patients

Vasopressor Use for Adult Septic Shock
(with guidance for steroid administration)

Initiate norepinephrine (NE) and titrate up to 35–90 μg/min to achieve MAP target 65 mm Hg

MAP target achieved

MAP target **not** achieved and judged poorly responsive to NE

Continue norepinephrine alone or add vasopressin 0.03 units/min with anticipation of decreasing norepinephrine dose

Add vasopressin up to 0.03 units/min to achieve MAP target[a]

MAP target achieved

MAP target **not** achieved

Add epinephrine up to 20–50 μg/min to achieve MAP target[b]

MAP target achieved

MAP target **not** achieved

Add phenylephrine up to 200–300 μg/min to achieve MAP target[c]

Fig. 9. A guide for vasopressor use for adult septic shock based on the 2016 Surviving Sepsis Campaign guidelines. IV, intravenous. [a] Consider IV steroid administration. [b] Administer IV steroids. [c] SSC guidelines are silent on phenylephrine. Notes: (1) Consider dopamine as niche vasopressor in the presence of sinus bradycardia. (2) Consider phenylephrine when serious tachyarrhythmias occur with norepinephrine or epinephrine. (3) Evidence based medicine does not allow the firm establishment of upper dose ranges of norepinephrine, epinephrine and phenylephrine and the dose ranges expressed in this figure are based on the authors interpretation of the literature that does exist and personal preference/experience. Maximum doses in any individual patient should be considered based on physiologic response and side effects. (*From* Dellinger RP, Schorr CA, Levy MM. A users' guide to the 2016 Surviving Sepsis Guidelines. Intensive Care Med 2017;3:301; with permission.)

with less severe forms of septic shock (patients with lower lactate levels, lower initial rates of norepinephrine infusion [5–15 μg/min], or if the patient was on only a single vasoactive agent at the time of vasopressin initiation) and for those who also received corticosteroids.[241–243] Vasopressin and corticosteroids may have a synergistic effect on maintaining MAP.[244] There may be a decreased need for renal replacement therapy when using vasopressin.[245] It is recommended in the current SSC guidelines to add vasopressin (up to 0.03 U/min) or epinephrine if an MAP $\geq$65 mm Hg is not achieved alone with norepinephrine. Vasopressin at 0.03 U/min can also be added to decrease the overall norepinephrine dosage.[97,98] The evidence behind these recommendations is weak and vasopressin was recently rebranded, increasing its average wholesale price by 50-fold, which may limit its utilization in some centers.[246]

Epinephrine was compared with norepinephrine infusion for critically ill patients requiring vasopressors (most of whom had sepsis) in one RCT and showed no difference in the time to achieving MAP goal, vasopressor-free days, or mortality. Epinephrine is associated with tachycardia and metabolic effects (lactic acidosis), which required stoppage of epinephrine in 12.9% in one study's patient population.[247] Another RCT compared epinephrine infusion with norepinephrine plus dobutamine for septic shock and showed no difference in time to achieving MAP goal, time to vasopressor withdrawal, SOFA score time course (resolution of organ dysfunction), or short-term and long-term mortality.[222] Last, data on phenylephrine for septic shock is relatively scarce, and the conclusions on its safety and efficacy in septic shock cannot currently be drawn.[248–250] Interestingly, when the United States experienced a norepinephrine shortage in 2011, phenylephrine was the most common vasopressor used as a replacement, and septic shock mortality increased during that time frame.[251]

Respiratory Failure and Ventilator Management

Essential to the management of the septic critically ill patient is an understanding of ventilator management. Established techniques for ventilated patients in the setting of acute respiratory distress syndrome (ARDS) are discussed first, followed by adjunct methods, and finally, the use of extracorporeal membrane oxygenation (ECMO). Other modes of ventilation, such as high-frequency ventilation, airway pressure release ventilation, and noninvasive ventilation strategies, are well described but this section is limited to techniques with proven mortality benefit in ARDS.

The ARDS Definition Task Force updated the categorization of ARDS with the objective of creating stages of ARDS that could be predictive of mortality. Instead of using changing nomenclature based on oxygenation parameters, they described ARDS on a continuum with worsening mortality as oxygenation worsened. Compared with the American-European Consensus Conference definition, the final Berlin Definition had better predictive validity for mortality.[252] The most widely accepted treatment for ARDS involves the utilization of lower tidal volumes to reduce lung injury and the subsequent inflammatory response. In a landmark study, which was terminated early due to clear mortality benefit, the death before discharge rate in the lower tidal volume group was 31% compared with 39.8% in the higher tidal volume group. Utilization of a 6 mL/kg of predicted body weight tidal volume was also associated with improvements in ventilator days, and more than a quarter of patients in each arm of the study were ventilated with a primary diagnosis of sepsis.[253] Previous and current SSC guidelines recommend a target tidal volume of 6 mL/kg predicted body weight in sepsis-induced ARDS and an upper limit goal for plateau pressures of 30 cm H_2O over higher plateau pressures with higher positive end-expiratory pressure (PEEP) over lower PEEP in patients with severe sepsis-induced ARDS.[95–98] A new recommendation is the use of lower tidal volumes over higher tidal volumes in patients with sepsis-induced respiratory failure without ARDS.[97,98] This new recommendation is based on recent studies that showed improved outcomes with low tidal volume ventilation in patients without ARDS, including decreased development of ARDS and decreased duration of mechanical ventilation, but no change in mortality.[254,255]

Prone positioning has shown to be beneficial in the setting of ARDS with low tidal volume settings. In a multicenter, prospective, randomized, controlled trial, Guerin and colleagues[256] showed that early prone positioning decreased 28-day mortality from 32% to 16% and 90-day mortality from 41.0% to 23.6%. Patients who had ARDS and Pao_2/Fio_2 less than 150 were placed in a prone position or standard supine position within the first 36 hours of intubation. The prone group was positioned for

more than 16 consecutive hours each day until they met predefined oxygenation improvement requirements. The 2012 SSC guidelines recommended using prone over supine positioning in adult patients with sepsis-induced ARDS and a Pao_2/Fio_2 ratio less than 100.[95,96] This was changed to a Pao_2/Fio_2 ratio less than 150 in the newest guidelines.[97,98] A recent meta-analysis concluded there is a reduced mortality with prone compared with supine position for ARDS but is associated with an increase in pressure sores.[257]

Neuromuscular blockade in the setting of ARDS can improve gas-exchange, and Papazian and colleagues[258] further demonstrated a mortality benefit. In this multicenter, double-blind trial, patients with early ARDS and Pao_2/Fio_2 ratio less than 150 were randomized to high fixed dose cisatracurium besylate or placebo, with each group using low tidal volume ventilator settings: 28-day mortality improved from 33.3% to 23.7% in the neuromuscular blockade group and 90-day mortality improved from 40.7% to 31.6% with the addition of cisatracurium. This benefit was confined to the patients whose Pao_2/Fio_2 ratio was less than 120. Thus, these patients would be included in the moderate and severe Berlin stages of ARDS.[252] The most recent SSC guidelines give a weak recommendation for using neuromuscular blocking agents for ≤48 hours in adult patients with sepsis-induced ARDS and Pao_2/Fio_2 ratio less than 150.[97,98]

An evolving strategy in ARDS and sepsis is the use of ECMO. Peek and colleagues[259] published results of the CESAR trial in 2009, which was a multicenter trial comparing ECMO with conventional management. In their trial, the ECMO group had 63% 6-month survival compared with 47% in the conventional ventilator group. The conventional ventilator group included many patients who did not receive low tidal volume ventilation, so the true benefit of ECMO in the setting of current ARDS standard-of-care treatment remains to be seen.

Nutrition

Nutrition in the critically ill population is a complex issue that encompasses enteral options, parenteral options, and other supplements.[260] Robust caloric intake has been shown to improve the mortality of both the underweight and the overweight populations.[261] The preferred route for nutrition in the critically ill population is via enteral access. This becomes challenging in the setting of mechanical ventilation, where nutrition must come through means of enteric tubes. A randomized multicenter trial was conducted to determine whether trophic feeding was superior to full enteral feeding and the results showed no difference in mortality, infectious complications, or ventilator-free days between the groups.[262] Dispelling other common myths with regard to enteral nutrition, a recent systematic review showed no utility of measuring gastric residuals in the medical intensive care population. There was an increased association with aspiration in surgical patients with gastric residuals greater than 200 mL, so this must be considered when treating specific patient populations.[263] Acosta-Escribano and colleagues[264] helped solve another quandary in the area of enteral nutrition: transpyloric versus gastric feeding. In their prospective randomized study, they evaluated patients who received either transpyloric or gastric feeds. In their study, the transpyloric group had improved rates of pneumonia and had a higher total caloric intake, supporting the use of transpyloric feeding. This was further supported by a recent Cochrane review showing a 30% reduction in pneumonia rates in those patients who were fed past their pylorus.[265]

In those patients who cannot receive enteral nutrition, another option is parenteral nutrition. Parenteral nutrition carries many risks, including bloodstream-related infections, and the risk of such infections increases as the parenteral caloric intake

increases.[266] Later initiation of parenteral nutrition therapy is actually associated with fewer complications, decreased ventilator days, and a cost savings with regard to early parenteral nutrition therapy.[267] When early enteral therapy is compared with early parenteral nutrition therapy, mortality was similar, but enteral nutrition had lower complication rates.[268] The current SSC guidelines recommend against the early administration of parenteral nutrition (based on no mortality benefit and increased cost and risk of infection) and to instead initiate intravenous glucose and advance enteral feeds as tolerated in the first 7 days in critically ill patients with sepsis or septic shock in whom early enteral feeding is not possible.[97,98]

Other supplements, such as glutamine, selenium, and other antioxidants, are being actively studied, but clear benefit to these supplements remains to be seen.[269–271] Clinical trials on omega-3 supplementation has not confirmed clinical benefit in patients who are critically ill or patients with ARDS.[272,273]

Fluid and Kidney Management

Discussions on the genitourinary system include the choice of fluids, acute kidney injury, fluid balance, diuresis, ultrafiltration, and the management of acidosis. Crystalloid and albumin are generally accepted as the resuscitation fluid of choice for sepsis and septic shock resuscitation. A systematic review and meta-analysis showed increased risk of death and increased need for renal replacement therapy when resuscitated with hydroxyethyl starches and their use is not recommended.[274,275] In a multicenter, randomized, double-blinded trial of ICU patients, the use of albumin was compared with saline for resuscitation. In the analysis, data on mortality, ventilator days, and total hospital stay were equivocal between the 2 groups. Albumin was found to be safe and equally as effective as 0.9% saline in the resuscitation.[276] The use of albumin was revisited in the severe sepsis population, and there was still no mortality benefit compared with crystalloid-based resuscitation at 28 or 90 days.[277] Yet in other meta-analyses of resuscitation in sepsis, albumin administration was found to have a mortality benefit compared with crystalloid resuscitation.[278,279] Correcting hypoalbuminemia (goal >3 g/dL) appears to decrease morbidity.[280] Currently, the expense of colloid limits its utilization, but the current SSC guidelines do make a weak recommendation to use albumin in addition to crystalloids in initial resuscitation when patients require "substantial" amounts of crystalloids to limit harmful fluid overload (see **Fig. 5**).[97,98,101,102]

Positive fluid balance is deleterious in the setting of sepsis and septic shock. In multiple analyses, late positive fluid balance was an independent risk factor for mortality.[281–284] Fluid should be restricted in the later stages of sepsis. Diuretics are widely used to reduce fluid overload. Unfortunately, the PICARD group showed a significant increase in both death and loss of renal recovery in patients who received diuretic therapy, thus diuretics should be used judiciously.[285] Improved net negative fluid balance and oxygenation occur when albumin is given concurrently with loop diuretics and this may protect against hypotension and need for vasopressors during diuresis.[286,287]

Metabolic acidosis is common in patients with sepsis or septic shock, and those who have a persistent metabolic acidosis are more often nonsurvivors than those patients who normalize.[288] Direct buffering of acidosis with bicarbonate has been more widely used, but in 1990, a prospective randomized study was performed showing that sodium bicarbonate had no positive effects on hemodynamics in patients with lactic acidosis.[289] This was further studied in 2009 in septic shock, and bicarbonate infusion had some benefit with regard to ICU length of stay and ventilator weaning, but there was no mortality benefit associated with its use.[290] Bicarbonate use is not

recommended in patients with hypoperfusion-induced lactic acidemia with pH $\geq$7.15.[97,98]

Acute kidney injury (AKI) is a common insult in sepsis, and there is a wealth of information on the prevention and treatment of AKI.[291] An evolving practice is the use of renal replacement therapy (RRT). The degree of lactic acidosis at the initiation of RRT has not been shown to correlate with mortality.[292] In a multicenter randomized trial, Gaudry and colleagues[293] showed that there is no mortality benefit of initiating early RRT, although many of these patients were nonseptic. Current SSC guidelines recommend using RRT only in patients with definitive indications for dialysis and give a weak recommendation for using continuous RRT to facilitate management of fluid balance in hemodynamically unstable patients with sepses.[97,98] There currently appears to be no benefit of intermittent over continuous RRT with regard to hemodynamics or mortality.[294]

Corticosteroids

In those critical care patients in septic shock, the prevailing endocrine topics involve steroid use in adrenal suppression and glycemic control. Put simply, if you suspect adrenal suppression in patients with vasopressor requirements, then steroids can be given. In general, release of cortisol increases and cortisol metabolism decreases in periods of stress, whether that be infection, trauma, burns, or surgery.[295] The hypothalamic-pituitary-adrenal axis can be impaired during severe illness, and this can be manifested clinically. In those patients with hypotension refractory to vasopressor therapy, 200 mg of hydrocortisone in 24 hours can be given empirically or for those patients with a random cortisol level below 15 μg per deciliter. For intermediate cortisol levels, steroids also can be considered.[296] Although these guidelines are in place and are widely used, the utility of such treatment has come into question with the results of the CORTICUS trial,[297] the HYPRESS trial,[298] and a meta-analysis by Gibbison and colleagues,[299] which, in general, showed a shorter time to shock reversal with hydrocortisone use but no survival benefit.

Glycemic Control

Glycemic control without hypoglycemia improves outcomes and should be achieved if possible. The goal for an upper target should be $\leq$180 mg/dL via an arterial blood sample if possible, which is more accurate than point of care capillary blood glucose testing.[97,98,300] Hyperglycemia is widely associated with worse outcomes in the perioperative period in those patients with critical illness. Egi and colleagues[301] showed a 3.85 odds ratio of mortality in those nondiabetic ICU patients whose blood glucose exceeded 200 mg/dL. Moreover, the correction of hyperglycemia improves rates of infection, reoperation, anastomotic failure, and death in the general surgical population.[302] With this information, it follows that tight insulin control could improve patient outcomes even further. Van den Berghe and colleagues[303] showed improvements in both ICU survival as well as in-hospital survival if tight glucose control (target 80–110 mg/dL) was achieved. This was confuted by the NICE-SUGAR trial, which showed that intensive glucose control increased mortality among adults in the ICU.[304]

A meta-analysis by Griesdale and colleagues[305] showed intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, patients in surgical ICUs appeared to benefit from intensive insulin therapy (relative risk 0.63, 95% confidence interval [CI] 0.44–0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12). Additional review of intensive insulin therapy (80–110 mg/dL) appeared beneficial in critically ill surgical patients but

requires frequent measurement of glucose to avoid hypoglycemia.[306] As such, efforts should be mounted to tighten glucose control while preventing hypoglycemia. Balanced nutrition is protective from hypoglycemia and if there is no nutritional source, we recommend protective D10 W at 30 mL/h[307] Manual titration of insulin infusion therapy is prone to variability and it is difficult to measure compliance and we advocate a computerized protocol. This is supported by the results of Dortsch and colleagues[308] who compared a computerized insulin infusion titration protocol to a manual titration and showed significantly improved overall glucose control and significantly reduced hypoglycemic episodes with the computerized protocol.

SUMMARY

The new definitions of sepsis and septic shock reflect the inadequate sensitivity, specify and lack of prognostication of SIRS criteria.[10,16] SOFA more effectively prognosticates in sepsis and critical illness. Understanding the pathophysiology of sepsis improves understanding of why organ dysfunction occurs and offers opportunities for intervention. Three therapeutic principles most substantially improve organ dysfunction and survival in sepsis: (1) early, appropriate antimicrobial therapy; (2) restoration of adequate cellular perfusion; and (3) timely source control. Mortality from sepsis and septic shock has been greatly reduced over time from following these principles.[6] The timing and appropriateness of antibiotic therapy is vitally important. Antibiotic stewardship prevents resistance development and subsequent complex infections. It is clear that early quantitative resuscitation strategies impact a mortality reduction in sepsis and help define a hemodynamic phenotype of the patient.[133] Dynamic measures of fluid responsiveness should be used to help avoid unnecessary positive fluid balances, which result in poorer outcomes. We recommend ICU protocols that follow the models of the ABCDEF bundle[205–207] and follow the evidence-based SSC[97,98] and the European Society of Intensive Care Medicine[134] evidence-based expert consensus recommendations with regard to hemodynamic monitoring, fluid resuscitation, choice of vasoactive agents and inotropes, hydrocortisone use, and glycemic control without hypoglycemia.

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