Current Treatment of Severe Sepsis

Ismail Cinel, MD, PhD, and R. Phillip Dellinger, MD

Corresponding author
R. Phillip Dellinger, MD
Section of Critical Care Medicine, Cooper University Hospital, One Cooper Plaza, 393 Dorrance, Camden, NJ 08103, USA.
E-mail: dellinger-phil@cooperhealth.edu

Current Infectious Disease Reports 2006, **8:**358–365
Current Science Inc. ISSN 1523-3847

The treatment of severe sepsis includes three essential principles: eradication of the inciting infection using source control measures and empiric antibiotics, hemodynamic resuscitation of hypoperfusion to avoid acute life-threatening organ dysfunction, and sustained support of organ system dysfunction using interventions that minimize organ injury. Therapy can be divided into immediate steps taken to stabilize the patient, followed by more definitive therapeutic intervention. The evidence for best clinical practice for resuscitation, management of infection, and intensive care unit supportive care has recently been synthesized by the Surviving Sepsis Campaign and published as evidence-based guidelines for the management of severe sepsis and septic shock.

Introduction

In recent years, significant progress has been made to develop a more standard approach to the management of severe sepsis in the areas of tissue hypoperfusion and organ dysfunction [1,2••]. The progress has been prompted by recent positive clinical trials and the attempt to codify traditional principles of management as they relate to antibiotics and source control.

Empiric Antibiotic Therapy and Source Control

The key to ensuring survival in severe sepsis is the combination of rapid removal of infected tissue or devices and antibiotic treatment. Selecting initial antibiotics that cover the infecting organism is a high priority in sepsis. Antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained [2••,3]. A progressive increase in mortality has been demonstrated with increasing delays in therapy. Still, only 50% of septic shock patients receive effective antimicrobial therapy within 6 hours of documented hypotension [4•]. Emergency departments (EDs) and critical care units should keep a supply of premixed antibiotics available to help ensure that antimicrobial agents will be infused promptly. Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of sepsis. Drug choice should be guided by the susceptibility patterns of microorganisms in the community and the hospital.

As empiric therapy for severe sepsis or septic shock, monotherapy, especially with carbapenems and third- or fourth-generation cephalosporins, is as efficacious as combination therapy with a ß-lactam and an aminoglycoside. However, the initial use of a combination of two antibiotics has some advantages. It broadens the antibacterial spectrum, and it may exert additive or synergistic effects against the infecting pathogen and reduce the emergence of resistant bacteria or superinfections [3]. Early coverage is broad in this strategy, but it can and should be streamlined following the return of culture results. Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy. The duration of therapy should typically be 7 to 10 days, depending on clinical response.

Despite the initially broad treatment strategy, every effort should be made to restrict the number of antibiotics and narrow the spectrum of antimicrobial therapy in order to minimize the development of resistant pathogens, contain costs, and reduce toxicity. To this end, clinicians should use microbiologic and clinical data to reassess the antimicrobial regimen after 48 to 72 hours. Importantly, if by 3 days, cultures do not support a diagnosis of infection as the cause of a systemic inflammatory response, systemic antibiotics should be discontinued to reduce the risk of superinfection with resistant species, and the patient should be reevaluated with repeat cultures as indicated.

Some general guidelines exist for choosing antibiotic therapy. In patients with severe sepsis without an identifiable source, broad-spectrum coverage can include combining antipseudomonal cephalosporin or antipseudomonal penicillin with an aminoglycoside or fluoroquinolone. When anaerobes are suspected as a possible cause and an antipseudomonal cephalosporin is used, clinicians should consider adding metronidazole or clindamycin. On the other hand, if *Pseudomonas aeruginosa* is a possible cause, imipenem or meropenem as single agents offer broad coverage and may be combined with

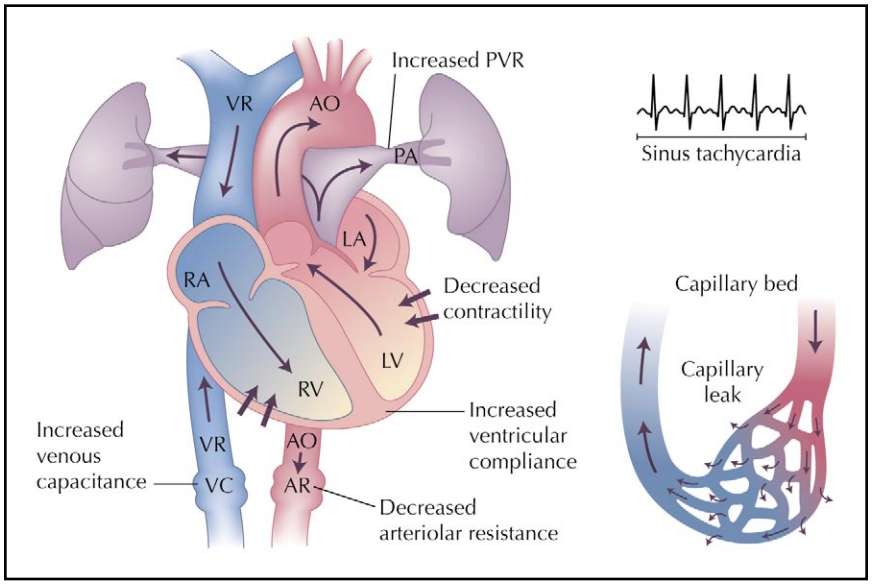

Figure 1. Cardiovascular changes associated with septic shock. AO—aorta; AR—arteriolar resistance; LA—left atrium; LV—left ventricle; PA—pulmonary artery; PVR—pulmonary vascular resistance; RA—right atrium; RV—right ventricle; VC—venous capacitance; VR—venous return. (*From* Dellinger [18]; with permission.)

an aminoglycoside or fluoroquinolone to provide double antipseudomonal drug coverage.

Staphylococcus aureus is the most frequent microorganism isolated in infections acquired in hospitals and intensive care, and the emergence of methicillin resistance (MR) is a main feature of the nosocomial pathology. The cost and increased hospital stay due to *S. aureus* are significant, but increased mortality is questionable in patients with MRSA bacteremia [5]. MRSA isolates show a high level of resistance to antibiotics (80% macrolides and 90% quinolones). Reduced MRSA susceptibility to vancomycin has been reported (ie, vancomycin-intermediate *S. aureus*/vancomycin-resistant *S. aureus* [VISA/VRSA]) [6]. Treatment of MRSA infections with glycopeptides (eg, vancomycin, teicoplanin) has had modest efficacy, especially in pulmonary infection [7], whereas linezolid, quinupristin-dalfopristin, and daptomycin are therapeutic alternatives with good clinical efficacy.

Linezolid binds to the ribosome and inhibits microbial protein synthesis, providing an antimicrobial activity independent of the resistance status toward other antibiotics [8]. Linezolid is particularly effective against MRSA and glycopeptide-resistant *S. aureus* and has a good penetration into lung compartments [9]. In one study, linezolid was compared to vancomycin when only ventilator-associated pneumonia (VAP) by MRSA was a component of severe sepsis. Linezolid was associated with significantly higher rates of clinical cure (62.9% vs 21.2%, $P = 0.001$), survival (84.1% vs 61.7%, $P = 0.02$), and eradication (60.5% vs 22.9%, $P = 0.001$) [10•]. In addition, similar rates of clinical cure and microbiologic eradication were found for linezolid and teicoplanin [11]. These data suggest that linezolid is probably the best alternative for the treatment of nosocomial pneumonia by MRSA. Furthermore, it has been shown that even though linezolid is significantly more expensive than vancomycin, it is still a cost-effective alternative in VAP [12]. However, no dramatic superiority has been demonstrated with quinupristin-dalfopristin and daptomycin in the MRSA infections compared with standard therapy.

A number of new compounds highly active in vitro against *S. aureus* are under current investigation in phase II trials. For example, compared to vancomycin, a single daily dose of dalbavancin demonstrated a significantly higher overall success rate in treating catheter-related sepsis by gram-positive pathogens such as MRSA [13].

Empiric antifungal therapy should not be used routinely in all patients with severe sepsis or septic shock, but it may be justified in selected subsets of septic patients at high risk for invasive candidiasis. In a large multicenter trial that included 239 patients with invasive candidiasis (of whom 24 were neutropenic), treatment with echinocandins (caspofungin) was as effective as and better tolerated than amphotericin B deoxycholate [14]. Importantly, prospective cohort studies showed that mortality was 1.4 to 8 times higher when initial antibiotic therapy of fungal infection was inadequate [15,16].

Source control, an essential component of the early management of severe sepsis, is therapy that targets the focus of an infection unlikely to be cleared with antibiotics alone. Cardinal principles of source control include drainage of infected fluid collections, debridement of infected solid tissue, and removal of a device or foreign body. The benefits of removing a device must be weighed against the risks and the ease of removal [17]. Infections of the abdomen, thorax, and sinuses may require source control measures. These measures should be instituted as soon as possible after identification of the focus and initial resuscitation.

Initial Resuscitation of Sepsis-induced Tissue Hypoperfusion

When sepsis induces inadequate tissue perfusion, the delivery of oxygen and other nutrients to tissue beds declines, causing cellular and organ dysfunction. A

complex interaction exists between pathologic vasodilatation, relative and absolute hypovolemia, direct myocardial depression, and altered blood flow distribution, which occur as a consequence of the inflammatory response to infection, especially in septic shock (Fig. 1) [18]. Cellular injury and organ injury have been shown to occur as a direct consequence of both the inflammatory response in sepsis and hypoperfusion. The presence of significant hypotension or evidence of cellular hypoxia (lactic acidosis) requires immediate assessment of oxygen delivery. Inadequate tissue oxygenation may exist in the absence of lactic acidosis and overt hypotension. Lactic acidosis may also exist in the presence of increased oxygen delivery and would not be amenable to further hemodynamic resuscitation in this case. Rapid stabilization of the patient's hemodynamic status, including volume expansion and administration of combined vasopressors/inotropes titrated to selected endpoints of resuscitation, is essential to limit additional organ injury and to restore organ function [19].

Clinically useful global markers of tissue perfusion include hypotension (ie, mean arterial pressure [MAP] below 65–70 mm Hg in adults), acid-base status (base excess and blood lactate), and the mixed venous or central venous oxygen saturations. Poor tissue perfusion may be manifest clinically by reduced capillary refill, oliguria, and altered sensorium. The adequacy of regional perfusion is usually assessed by evaluating indices of specific organ function. However, none of these markers have been validated as a reliable indicator of adequate resuscitation, and they may occur or progress despite adequate tissue oxygen delivery.

Some variables are potential endpoints for the resuscitation process and provide information about response to treatment in severe sepsis. These variables, listed in order of likely importance, include arterial blood pressure, intravascular volume status, cardiac output, mixed venous oxygen saturation (SvO_2), central venous oxygen saturation ($ScvO_2$), blood lactate levels, and the measurement of regional perfusion by gut tonometry or sublingual capnometry [20]. In septic shock, accurate and continuous measurement of arterial blood pressure is essential. Additionally, central venous catheters are needed to infuse vasopressors and provide measurement of central venous pressure (CVP) and superior vena cava oxyhemoglobin saturation, at a minimum.

Fluid resuscitation should be initiated immediately after finding evidence of tissue hypoperfusion (ie, hypotension, elevated lactate, or low urine output). To reverse organ hypoperfusion in severe sepsis, one must initially increase left ventricular preload with volume therapy in order to increase stroke volume. Signs of global tissue dysoxia and tissue hypoperfusion should decrease with fluid resuscitation [19]. Limits of fluid resuscitation are guided by central filling pressures or the development of hypoxemia.

When crystalloids and colloids are titrated to the same level of filling pressure, they restore tissue perfusion to the same degree and are equally effective for resuscitation. Because of their propensity for leakage into the extravascular space, approximately three times larger volume of crystalloid is required than colloid to achieve the same effect, and slightly longer infusion periods may be necessary to reach comparable hemodynamic endpoints. Crystalloids are usually favored for fluid resuscitation, since they cost significantly less than colloids. Besides cost considerations, the choice between the two may be influenced by their effects on variables such as coagulation and renal function, although further studies are needed to clarify their impact on outcome. The prospective, controlled, randomized, double-blind Saline versus Albumin Fluid Evaluation (SAFE) trial of fluid replacement in 7000 critically ill patients showed no difference in mortality between crystalloids and albumin, although subgroup analysis revealed that albumin may have some benefit in severe sepsis patients [21]. This topic has prompted continued investigation. An ongoing trial called Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients (CRISTAL) is comparing synthetic colloids with crystalloids. For now, crystalloids and synthetic colloids can be used alone or in combination.

Fluid challenge in patients with suspected inadequate arterial circulation may be given at a rate of 500 to 1000 mL of crystalloids or 300 to 500 mL of colloids over 30 minutes. It may be repeated based on increase in blood pressure (to maintain a MAP of > 70 mm Hg and a heart rate < 110 beats/min) and urine output, while avoiding the development of clinically significant pulmonary edema. We typically choose a CVP target of 8 to 12 mm Hg or a pulmonary artery occlusion pressure of 12 to 16 mm Hg. High filling pressures may be needed in the presence of mechanical ventilation or a stiff or hypertrophied left ventricle. The degree of intravascular volume deficit in patients with severe sepsis varies, and input/output ratio is of no utility to judge fluid resuscitation needs during the first 24 hours of management. In the course of septic shock, fluid resuscitation should be commenced as early as possible with the guidance of CVP even before intensive care unit (ICU) admission.

Dopamine and norepinephrine are the two vasopressor agents of choice for patients who do not respond to fluid resuscitation. Though it is still unclear whether one drug is superior to the other, a prospective, randomized European study is ongoing to evaluate the effects of dopamine versus norepinephrine as the initial vasopressor agent in shock. Additionally, lower than expected plasma levels of vasopressin have led to the consideration that low doses of vasopressin (0.01–0.04 μg/min) be added to standard doses of norepinephrine or dopamine therapy in septic shock patients [22]. In those patients requiring high-dose or increasing vasopressor therapy within the first 8 hours of septic shock, low-dose steroids are recommended.

$ScvO_2$ measurements provide useful information to evaluate the complex relation between intravascular blood

volume and cardiac function. When the $ScvO_2$ remains low despite obtaining CVP and MAP targets, clinicians should consider packed red blood cells to achieve a hematocrit of greater than 30% or dobutamine (up to maximum of 20 μg/kg/min). One proposed strategy—increasing cardiac index to reach a predefined elevated level—seems ineffective and potentially harmful and is not recommended [23,24]. Achieving adequate MAP and oxygen delivery may still be ineffective in improving adequate tissue oxygen metabolism and organ function. Therapy should be tailored according to its effect on elevated blood lactate or low $ScvO_2$ as part of a management algorithm [25].

Even after global optimization of conventional hemodynamic and oxygen-derived parameters, regional hypoperfusion abnormalities such as increased heterogeneity of microvessel perfusion can persist in septic shock. Some professionals have proposed a perfusion-based scoring system, including gastric intramucosal pH, sublingual CO_2 gap, and sublingual microvascular perfusion using orthogonal polarization spectral imaging for shock recognition [26]. Persistent microvascular alterations in septic shock are related to the development of multiple organ failure and death [27]. In this study by Sakr et al. [27], the degree of improvement in small-vessel perfusion over the first 24 hours of therapy was a good predictor of mortality, suggesting that the capacity to impact clinical outcome via restoration of microcirculatory perfusion may be time sensitive. Therapeutic modalities that improve microvascular function are also associated with decreased organ dysfunction and improved outcome in patients with sepsis [28,29]. Additionally, recent data has demonstrated that improvement in cardiovascular ($P = 0.001$), renal ($P < 0.0001$), or respiratory ($P = 0.0469$) function from baseline to day one is predictive of increased survival at day 28 [30•]. A direct link can be made between increasing vasopressor use and rising creatinine level at day one with mortality at day 28.

Novel agents that might augment microcirculatory blood flow include vasodilators, as well as agents that would modulate endothelial cell surface function. De Backer et al. [31] showed that a marked impairment of sublingual microcirculatory blood flow in patients with septic shock was reversible with local administration of acetylcholine, indicating the endothelium in septic shock is still responsive to mediators of vascular tone. Spronk et al. [32] demonstrated a severe impairment in sublingual microcirculatory blood flow that was improved with an infusion of nitroglycerin. Clinicians should note that vasodilator interventions may worsen arterial hypotension. The protocol in a randomized controlled trial of early goal-directed therapy included nitroglycerin for a MAP greater than 90 mm Hg [19]. However, this was in patients with elevated blood pressure. In that same protocol, dobutamine was used to increase $ScvO_2$ less than 70% after correction of CVP, MAP, and hematocrit during the first 6 hours of treatment. Although dobutamine-associated increases in macrocirculatory blood flow in sepsis are well acknowledged, it was recently shown that 5 μg/kg/min dobutamine improved microcirculatory perfusion in septic patients but failed to normalize it [33]. Although still experimental, further research could demonstrate vasodilatory compounds to be more effective than dobutamine for improving microcirculatory blood flow [26,34].

Support of Organ System Dysfunction

Glucocorticoids

Glucocorticoids exert key actions during sepsis, interacting with metabolism and immune and cardiovascular systems. Regarding the major anti-inflammatory properties, the first evaluations of glucocorticoids in severe sepsis were done with high doses, and corticotherapy was abandoned during the 1980s after several studies showed no benefit on outcome [35]. A meta-analysis of nine prospective, randomized, controlled studies concluded that glucocorticoids have no favorable effect on morbidity and mortality in severe sepsis and may even cause an increased risk for superinfection-related death [36].

Since then, the use of glucocorticoids has been reconsidered and has become a standard of care since adrenal dysfunction was found to be an aggravating factor during septic shock. Two reviews of recent randomized trials showed that a replacement therapy with a long course of low-dose corticosteroids (200–300 mg/d hydrocortisone for 7 days) improved systemic hemodynamics, duration of shock, and survival [37,38]. It was recommended that clinicians systematically assess adrenal function with a short adrenocorticotropic hormone (ACTH) test and give corticosteroids only to patients with a random cortisol concentrations greater than 15 μg/dL or blood cortisol level between 15 and 34 μg/dL and an increment in cortisol level of 9 μg/dL or less after 250 μg of ACTH [39]. However, it remains difficult to provide definite recommendations for the selection of patients who might benefit most from corticosteroid treatment, and exploration of the hypothalamic-pituitary-adrenal axis as part of the decision-making process is controversial.

In the end, several questions still need to be answered on this topic. Does corticoid therapy give advantage in septic shock only to patients with adrenal insufficiency? And can these patients be readily identified? Is early treatment better than late treatment? What is the best duration of therapy?

Recombinant human activated protein C

Realization of the links between the coagulation system and the immune response to sepsis led to the development of recombinant human activated protein C (rhAPC) [28]. Other anticoagulants such as tissue factor pathway inhibitor [40] and antithrombin III [41] have had little effect on mortality in sepsis. However, the mechanisms of rhAPC appear to extend beyond its anticoagulant activity to include antiapoptotic activity, as shown by Joyce et al. [42], and affect endothelial protein C receptor, which is present in

endothelial cells, neutrophils, and monocytes [43]. The rhAPC Worldwide Evaluation in Severe Sepsis (PROWESS) trial (n = 1690) showed a 6.1% absolute reduction in mortality and an increase in incidence of serious bleeding at 28 days among adults with severe sepsis treated with 24 μg/kg/h of drotrecogin alfa (activated) for 96 hours [28]. In November 2001, the U.S. Food and Drug Administration (FDA) approved rhAPC for adults with severe sepsis and a high risk of death (such as an acute physiology and chronic health evaluation [APACHE II] score ≥ 25). Surviving Sepsis Campaign (SSC) guidelines recommend the use of rhAPC in patients with high risk of death due to sepsis-induced organ dysfunction. The guidelines identified four such situations: acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, and APACHE II ≥ 25 [2••]. The Extended Evaluation of Recombinant Activated Protein C (ENHANCE) trial provided evidence to support the favorable benefit/risk ratio observed in the PROWESS trial and suggested that earlier therapy was more effective [44]. On the other hand, this study also revealed a greater incidence of serious hemorrhage with rhAPC than was evident in the PROWESS trial.

The pediatric trial in severe sepsis patients was stopped based on futility after approximately 400 patients had been enrolled [45]. Additionally, the results of the Administration of Drotrecogin alpha (activated) in Early Stage Severe Sepsis (ADDRESS) trial, designed with the purpose of prospectively studying the effect of rhAPC in severe sepsis patients with a clinical assessment of low risk of death, supported the FDA labeling that rhAPC was not of utility in severe sepsis patients with a clinical assessment of low risk of death (defined by an APACHE II score < 25 or single-organ failure) [46]. ADDRESS trial results suggest that an APACHE II ≥ 25 may not always represent high risk of death when the initial overall clinical assessment is indicative of low risk of death. Ideally, when administering rhAPC, clinical assessment of high risk of death would be made by a seasoned critical care clinician with an understanding and knowledge of severe sepsis and rhAPC clinical trial results, who would weigh the risk/benefit ratio in that patient [47].

Strict control of blood glucose by intensive insulin therapy

Based on the rationale that mild elevations were not deleterious and tight control might be complicated by life-threatening hypoglycemia, insulin has traditionally not been administered until blood glucose levels exceeded 180 to 200 mg/dL. In a 2001 study, strict control of blood glucose (ie, maintaining blood glucose between 80 and 110 mg/dL) reduced ICU mortality from 8% to 4.6% in a large surgical ICU population [48]. In this study, all subjects received intravenous glucose and parenteral nutrition immediately postoperatively. A subsequently published observational study from a single-center medical-surgical ICU suggested that intensive insulin therapy improved outcome [49]. Additionally, intensive insulin therapy was recently associated with substantial cost savings over conventional therapy [50]. Glycemic control has been reported to produce endothelial protection, reduction of systemic inflammation, and protection of mitochondrial function, all possible explanations why strict control of glucose would be beneficial [51–53]. The protocol used to achieve glucose control appeared safe in the studies referenced above, as evidenced by a low incidence of hypoglycemia [48,49]. However, the multicenter Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, designed to randomize 600 subjects with medical and surgical severe sepsis to conventional or intensive insulin therapy, was stopped after recruitment of 488 subjects, because of no difference in mortality (21.9% vs 21.6%, $P = 1.0$) and frequent hypoglycemia in the intensive insulin therapy arm (12.1% vs 2.1%, $P < 0.001$) [54].

A recently published large clinical trial in medical ICU patients demonstrated that hypoglycemia occurred more often in medical ICU patients than in the surgical ICU patients, and although reduction of morbidity was achieved, reduction of mortality was not [55•]. Two ongoing large-scale, multicenter, randomized trials are examining the issue of glycemic control in the ICU: the GLU-Control study, which will enroll 3500 patients, and the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) which will enroll 4500 patients. Until those trials conclude, physicians must interpret the available data in the context of their clinical practice [56].

Protective lung ventilation strategies with the impact of spontaneous breathing

It is now widely accepted that mechanical ventilation itself can initiate or propagate acute lung injury (ALI) [57]. In sepsis patients who do not have ALI or ARDS at the time of intubation, tidal volume is also an important risk factor for the development of these two conditions during the course of mechanical ventilation [58]. The application of open-lung strategies, as proposed by Amato et al. [59], has improved outcomes in patients with ARDS, but the optimal setting of positive end-expiratory pressure is still controversial. The largest randomized, controlled trial enrolled 861 patients and documented a 9% absolute and 22% relative reduction in 28-day mortality for the group receiving a targeted tidal volume of 6 mL/kg predicted body weight (and a plateau pressure ≥ 30 cm H_2O) versus those receiving 12 mL/kg [57]. Adoption of 6 mL/kg tidal volume strategy into usual practice results in a mortality rate similar to that of the ARDSnet study [60].

An acceptable side effect of lung protective ventilation is permissive hypercapnia (hypercapnic acidosis), which has recently been shown to be protective against ventilator-associated lung injury with reduced 28-day mortality [61]. Additionally, an increase in respiratory drive and work of breathing was noted, as the tidal volume was

Table 1. Sepsis resuscitation and management bundles

Bundle	Elements
Sepsis resuscitation bundle	Measure serum lactate. Obtain blood cultures prior to antibiotic administration and administer broad-spectrum antibiotic within 3 hours of ED admission and within 1 hour of non-ED admission. In the event of hypotension and/or a serum lactate > 4 mmol/L: -deliver an initial minimum of 20 mL/kg of crystalloid or an equivalent amount of colloid, -apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP > 65 mm Hg. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L: -achieve a central venous pressure (CVP) of ≥ 8 mm Hg, -achieve a central venous oxygen saturation ($ScvO_2$) ≥ 70% or mixed venous oxygen saturation (SvO_2) ≥ 65%.
Sepsis management bundle	Assess for administering low-dose steroids (200–300 mg IV daily for 7 days) for septic shock, according to hospital protocol. Assess for administering for recombinant human activated protein C, according to hospital protocol. Maintain glucose control between 70–150 mg/dL. Maintain a median IPP < 30 cm H_20 for mechanically ventilated patients.

ED—emergency department; IPP—inspiratory plateau pressure; IV—intravenous; MAP—mean arterial pressure.

Table 2. Adjunctive strategies to improve sepsis outcomes

Position the patient in a semirecumbent (≥ 30°) position to prevent VAP.
Use daily spontaneous breathing trial to evaluate for ventilation discontinuation and a standardized weaning protocol.
Use sedation protocols; use sedation scores and retitrate daily to the minumum necessary dose.
Avoid neuromuscular blockers if possible. If they are necessary, intermittent dosing is preferred. If IV administration is necessary, retitrate daily and monitor the depth of blockade.
Use low-dose unfractionated heparin or low molecular weight heparin for DVT prophylaxis. If anticoagulation is contraindicated, use mechanical methods unless contraindicated.
Use histamine H2 receptor blockers or proton pump inhibitors for stress ulcer prophylaxis.
Continuous venovenous hemofiltration is equivalent to intermittent, but continuous offers easier management in hemodynamically unstable patients.
Although clinical trials have not demonstrated that adequate nutrition alters outcome, most consider it important to achieve. Enteral is preferred.

DVT—deep vein thrombosis; IV—intravenous; VAP—ventilator-associated pneumonia.

reduced from 8 to 5 mL/kg in patients receiving lung protective ventilatory strategy, highlighting the importance of patient-ventilator dyssynchrony [62]. If the airway pressures are not excessively high (peak inspiratory pressure ≥ 30 cm H_2O), keeping the tidal volume at 7 or 8 mL/kg may not be harmful when use of tidal volume of 6 mL/kg causes dyssynchrony and requires increased sedation and a paralytic agent. The importance of maintaining patient contribution to ventilation, even with severe lung disorders, is noted by recent data showing decreases in duration of mechanical ventilatory support, length of stay in ICU, and overall costs of care when spontaneous breathing is maintained during mechanical ventilation [63].

Use of Protocolized Care

The impact of fluids and vasopressors on reversing tissue hypoperfusion can likely be facilitated by use of evidence-based protocolized care. One such approach, recommended by the SSC, uses the sepsis bundle performance improvement program, which is based on selected recommendations from the SSC bundles for the management of severe sepsis and septic shock. This program recommends use of two sets of time-based goals in the treatment of severe sepsis: the first centered around resuscitation and the second called the management bundle (Table 1). These bundles represent indicators of performance, which should improve clinical outcome when achieved in a timely manner. The sepsis resuscitation bundle is scored over 6 hours and includes blood cultures, antibiotics, and early goal-directed therapy indicators. The sepsis management bundle is scored over the first 24 hours and involves low dose steroids, recombinant human activated protein C, strict control of blood glucose levels, and lung protective ventilation.

A recent publication showed the potential for successful local implementation of a protocol to improve outcome in sepsis-induced tissue hypoperfusion [64]. Effective antimicrobial administration within the first hour of documented hypotension (one of the 6-hour bundle elements)

is associated with increased survival to hospital discharge in adult patients with septic shock [4•]. In addition to initial resuscitation and first-day management, supportive therapy over the entire ICU stay is important (Table 2).

Conclusions

Despite recent therapeutic breakthroughs, much still needs to be done to improve our understanding of and treatment of sepsis. Mortality rates remain high in severe sepsis. In terms of management, the SSC guidelines have been an important advance to promote optimal care. Protocolized care is very important, especially in the early phase of disease. Large trials using our molecular knowledge toward the development of effective treatment strategies in sepsis must remain our top priority.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Dellinger RP: **Current therapy for sepsis.** *Infect Dis Clin North Am* 1999, **13:**495–509.
2.•• Dellinger RP, Carlet JM, Masur H, et al.: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32:**858–873.

The authors implemented a comprehensive evidence-based guideline in the treatment of severe sepsis and septic shock that can accept as the beginning of the protocolized care in sepsis.

3. Bochud PY, Bonten M, Marchetti O, Calandra T: **Antimicrobial therapy for patients with severe sepsis and septic shock: An evidence-based review.** *Crit Care Med* 2004, **32:** S495–S512.
4.• Kumar A, Roberts D, Wood KE, et al.: **Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.** *Crit Care Med* 2006, **34:**1589–1596.

A retrospective cohort study including 2731 adult patients with septic shock showed that effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge.

5. Cosgrove SE, Sakoulas G, Perencevich EN, et al.: **Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis.** *Clin Infect Dis* 2003, **36:**53–59.
6. Walsh TR, Howe RA: **The prevalence and mechanisms of vancomycin resistance in Staphylococcus aureus.** *Annu Rev Microbiol* 2002, **56:**657–675.
7. Cruciani M, Gatti G, Lazzarini L, et al.: **Penetration of vancomycin into human lung tissue.** *J Antimicrob Chemother* 1996, **35:**865–871.
8. Hancock RE: **Mechanisms of action of newer antibiotics for Gram-positive pathogens.** *Lancet Infect Dis* 2005, **5:**209–218.
9. Honeybourne D, Tobin C, Jevons G, et al.: **Intrapulmonary penetration of linezolid.** *J Antimicrob Chemother* 2003, **51:**1431–1434.
10.• Kollef MH, Rello J, Cammarata SK, et al.: **Clinical cure and survival in Gram-positive ventilator-associated pneumonia. Retrospective analysis of two double-blind studies comparing linezolid with vancomycin.** *Intensive Care Med* 2004, **30:**388–394.

This is an excellent investigation including 544 VAP patients that supports the superiority of linezolid in VAP by MRSA.

11. Cepeda JA, Whitehouse T, Cooper B, et al.: **Linezolid versus teicoplanin in the treatment of Gram-positive infections in the critically ill: a randomized, double-blind, multicentre study.** *J Antimicrob Chemother* 2004, **53:**345–355.
12. Shorr AF, Susla GM, Kollef MH: **Linezolid for treatment of ventilator-associated pneumonia: a cost-effective alternative to vancomycin.** *Crit Care Med* 2004, **32:**137–143.
13. Raad I, Darouiche R, Vazquez J, et al.: **Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens.** *Clin Infect Dis* 2005, **40:**374–380.
14. Mora-Duarte J, Betts R, Rotstein C, et al.: **Comparison of caspofungin and amphotericin B for invasive candidiasis.** *N Engl J Med* 2002, **347:**2020–2029.
15. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al.: **Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis.** *Crit Care Med* 2003, **31:**2742–2751.
16. MacArthur RD, Miller M, Albertson T, et al.: **Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial.** *Clin Infect Dis* 2004, **38:**284–288.
17. O'Grady NP, Alexander M, Dellinger EP, et al.: **Guidelines for the prevention of intravascular catheter-related infections.** *Clin Infect Dis* 2002, **35:**1281–1307.
18. Dellinger RP: **Cardiovascular management of septic shock.** *Crit Care Med* 2003, **31:**946–955.
19. Rivers E, Nguyen B, Havstad S, et al.: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345:**1368–1377.
20. Beale RJ, Hollenberg SM, Vincent JL, Parrillo JE: **Vasopressor and inotropic support in septic shock: An evidence-based review.** *Crit Care Med* 2004, **32:**S455–S465.
21. Finfer S, Bellomo R, Boyce N, et al.: **A comparison of albumin and saline for fluid resuscitation in the intensive care unit.** *N Engl J Med* 2004, **350:**2247–2256.
22. Patel BM, Chittock DR, Russell JA, Walley KR: **Beneficial effects of short-term vasopressin infusion during severe septic shock.** *Anesthesiology* 2002, **96:**576–582.
23. Hayes MA, Timmins AC, Yau EH, et al.: **Elevation of systemic oxygen delivery in the treatment of critically ill patients.** *N Engl J Med* 1994, **330:**1717–1722.
24. Bourgoin A, Leone M, Delmas A, et al.: **Increasing mean arterial pressure in septic shock: effects on oxygen variables and renal function.** *Crit Care Med* 2005, **33:**780–786.
25. Pinsky MR, Vincent JL: **Let us use the PAC correctly and only when we need it.** *Crit Care Med* 2005, **33:**1119–1122.
26. Spronk PE, Zandstra DF, Ince C: **Bench-to-bedside review: sepsis is a disease of the microcirculation.** *Crit Care* 2004, **8:**462–468.
27. Sakr Y, Dubois MJ, De Backer D, et al.: **Persistent microvasculatory alterations are associated with organ failure and death in patients with septic shock.** *Crit Care Med* 2004, **32:**1825–1831.
28. Bernard GR, Vincent JL, Laterre PF, et al.: **Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344:**699–709.
29. Vincent JL, Angus DC, Artigas A, et al.: **Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS trial.** *Crit Care Med* 2003, **31:**834–840.
30.• Levy MM, Macias WL, Vincent JL, et al.: **Early changes in organ function predict eventual survival in severe sepsis.** *Crit Care Med* 2005, **33:**2194–2201.

This article stresses the importance of early diagnosis and treatment in severe sepsis and the impact of therapeutics on the early improvement of organ failures and positive patient outcome.

31. De Backer D, Creteur J, Preiser JC, et al.: **Microvascular blood flow is altered in patients with sepsis.** *Am J Respir Crit Care Med* 2002, **166:**98–104.
32. Spronk PE, Ince C, Gardien MJ, et al.: **Nitroglycerin in septic shock after intravascular volume resuscitation.** *Lancet* 2002, **360:**1395–1396.
33. De Backer D, Creteur J, Dubois MJ, et al.: **The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects.** *Crit Care Med* 2006, **34:**403–408.
34. Buwaldo M, Ince C: **Opening the microcirculation: can vasodilators be useful in sepsis?** *Intensive Care Med* 2002, **28:**1208–1217.
35. Bone RC, Fisher CJ Jr, Clemmer TP, et al.: **Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome.** *Chest* 1987, **92:**1032–1036.
36. Cronin L, Cook DJ, Carlet J, et al.: **Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature.** *Crit Care Med* 1995, **23:**1430–1439.
37. Annane D, Bellissant E, Bollaert PE, et al.: **Corticosteroids for severe sepsis and septic shock: a systemic review and meta-analysis.** *BMJ* 2004, **329:**480–488.
38. Minneci PC, Deans KJ, Banks SM, et al.: **Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose.** *Ann Intern Med* 2004, **141:**47–56.
39. Annane D, Sebille V, Charpentier C, et al.: **Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.** *JAMA* 2002, **288:**862–871.
40. Abraham E, Reinhart K, Opal S, et al.: **Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial.** *JAMA* 2003, **290:**238–247.
41. Warren BL, Eid A, Singer P, et al.: **Caring for the critically ill patient. High dose antithrombin III in severe sepsis: a randomized controlled trial.** *JAMA* 2001, **286:**1869–1878.
42. Joyce DE, Gelbert L, Ciaccia A, et al.: **Gene expression profile of antithrombotic protein C defines new mechanisms modulating inflammation and apoptosis.** *J Biol Chem* 2001, **14:**11199–11203.
43. Taylor FB Jr, Stearns-Kurosawa DJ, Kurosawa S, et al.: **The endothelial cell protein C receptor aids in host defense against Escherichia coli sepsis.** *Blood* 2000, **95:**1680–1686.
44. Vincent JL, Bernard GR, Beale R, et al.: **Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment.** *Crit Care Med* 2005, **33:**2266–2277.
45. Eisenberg P: **Discontinuation of Study F1K-MC-EVBP, Investigation of Efficacy and Safety of Drotrecogin Alfa (Activated) in Pediatric Severe Sepsis [letter].** http://www.fda.gov/medwatch/safety/2005/xigris_dearHCP_4-21-05.htm. Accessed April 11, 2006.
46. Abraham E, Laterre PF, Garg R, et al.: **Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death.** *N Eng J Med* 2005, **353:**1332–1341.
47. Dellinger RP: **Recombinant activated protein C: decisions for administration.** *Crit Care Med* 2006, **34:**530–531.
48. van den Berghe G, Wouters P, Weekers F, et al.: **Intensive insulin therapy in critically ill patients.** *N Engl J Med* 2001, **345:**1359–1367.
49. Krinsley JS: **Effect of an intensive glucose management protocol on the mortality of critically ill adult patients.** *Mayo Clin Proc* 2004, **79:**992–1000.
50. van den Berghe G, Wouters P, Kesteloot K, Hilleman D: **Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients.** *Crit Care Med* 2006, **34:**612–616.
51. Hansen TK, Thiel S, Wouters PJ, et al.: **Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels.** *J Clin Endocrinol Metab* 2003, **88:**1082–1088.
52. Langouche L, Vanhorebeek I, Vlasselaers D, et al.: **Intensive insulin therapy protects the endothelium of critically ill patients.** *J Clin Invest* 2005, **115:**2277–2286.
53. Vanhorebeek I, De Vos R, Mesotten D, et al.: **Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients.** *Lancet* 2005, **365:**53–59.
54. Brunkhorst FM, Kuhnt E, Engel C, et al.: **Intensive insulin therapy in patient with severe sepsis and septic shock is associated with an increased rate of hypoglycemia— results from a randomized multicenter study (VISEP) [abstract].** *Infection* 2005, **33:**19–20.
55.• van den Berghe G, Wilmer A, Hermans G, et al.: **Intensive insulin therapy in the medical ICU.** *New Engl J Med* 2006, **354:**449–461.

This randomized controlled trial of intensive insulin therapy in medical ICU patients demonstrated an overall morbidity development, whereas survival benefit was suggested in those patients who remained in the ICU for 3 days or longer.

56. Angus DC, Abraham E: **Intensive insulin therapy in critical illness.** *Am J Respir Crit Care Med* 2005, **172:**1358–1359.
57. **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.** *N Engl J Med* 2000, **342:**1301–1308.
58. Gajic O, Dara SI, Mendez JL, et al.: **Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation.** *Crit Care Med* 2004, **32:**1817–1824.
59. Amato MB, Barbas CS, Medeiro DM, et al.: **Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome.** *N Engl J Med* 1998, **338:**347–354.
60. Kallet RH, Jasmer RM, Pittet JF, et al.: **Clinical implementation of the ARDS network protocol is associated with reduced hospital mortality compared with historical controls.** *Crit Care Med* 2005, **33:**925–929.
61. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER: **Hypercapnic acidosis and mortality in acute lung injury.** *Crit Care Med* 2006, **34:**1–7.
62. Kallet RH, Campbell AR, Dicker RA, et al.: **The effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome.** *Crit Care Med* 2006, **34:**8–14.
63. Putensen C, Muders T, Varelmann D, Wrigge H: **The impact of spontaneous breathing during mechanical ventilation.** *Curr Opin Crit Care* 2006, **12:**13–18.
64. Trezeciak S, Dellinger RP, Abate NL, et al.: **Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department.** *Chest* 2006, **129:**225–232.