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# Management of Severe Sepsis and Septic Shock

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## 1. Introduction

Severe sepsis (systemic inflammation secondary to infection combined with acute organ dysfunction) and septic shock (severe sepsis combined with hypotension not rectified by fluid resuscitation) are complex multifactorial medical conditions with significant associated morbidity and mortality, and are among the leading causes of death in the intensive care unit (ICU). Even with aggressive treatment, the mortality has been shown to be around 40 percent (Bernard et al., 1997) and in some studies has been reported to be as high as 71.9 percent (Sasse et al., 1995).

In 2001, Angus et al conducted a study of the incidence, cost, and outcome of severe sepsis in the United States of America; the results showed an incidence of 3 cases per 1,000 population, a mortality rate of 28.6 percent, and a cost of \$22,100 per case, giving an annual cost of \$16.7 billion (Angus et al., 2001). The same study showed that the number of deaths per year associated with severe sepsis is equal to that of acute myocardial infarction, yet myocardial infarction has attracted far more attention and funding in terms of treatment and management research, leaving sepsis a relatively unacknowledged problem. With severe sepsis having such a high incidence, high and increasing mortality rate, and high annual cost, it is becoming a prime target for research into improving diagnosis, management, and survival.

Reducing morbidity and mortality in severe sepsis and septic shock has been the primary goal of the Surviving Sepsis Campaign (SSC) – a global initiative developed by the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM) to raise awareness of sepsis among healthcare professionals and to improve and standardize the early diagnosis and treatment of sepsis (Welcome To The Surviving Sepsis Campaign Website, n.d.). Containing a number of the world's experts on sepsis, this campaign attempts to tackle various challenges in the diagnosis and management of sepsis. Some of the challenges lie in the complexity of the condition and the variability in the presentation and course of sepsis, with many of the symptoms being of a general nature and easily attributable to a number of other conditions and etiologies. This makes it quite difficult to create a standard clinical definition of sepsis. This lack of definitive criteria for a diagnosis of sepsis makes it easily misdiagnosed, and consequently improperly treated. If, however, a diagnosis of sepsis is made, it is often still made late and treatment is less effective if delayed. As is discussed later in this chapter,

Disorder	Criteria
Systemic Inflammatory Response Syndrome (SIRS)	At least two of the following: <ul style="list-style-type: none"><li>• Body temperature &gt;38.5°C or &lt;35.0°C</li><li>• Heart rate &gt;90 beats per minute</li><li>• Respiratory rate &gt;20 breaths per minute or PaCO<sub>2</sub>&lt;32 mmHg or a need for mechanical ventilation</li><li>• White blood cell count &gt;12,000/mm<sup>3</sup> or &lt;4,000/mm<sup>3</sup> or immature forms &gt;10 percent</li></ul>
Sepsis	<b>SIRS PLUS:</b> documented infection based on either of the following: <ul style="list-style-type: none"><li>• Culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism</li><li>• Focus of infection identified by visual inspection (e.g. a ruptured bowel with free air or bowel contents found in abdomen at surgery, or a wound with purulent discharge)</li></ul>
Severe Sepsis	<b>Sepsis PLUS</b> at least one of the following signs of organ hypoperfusion or organ dysfunction: <ul style="list-style-type: none"><li>• Areas of mottled skin</li><li>• Capillary refill time ≥3s</li><li>• Urinary output &lt;0.5mL/kg for at least 1 hour or renal replacement therapy</li><li>• Lactic acid levels &gt;2mmol/L</li><li>• Abrupt change in mental status or abnormal electroencephalogram (EEG)</li><li>• Platelet counts &lt;100,000/mL or disseminated intravascular coagulation (DIC)</li><li>• Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)</li><li>• Cardiac dysfunction (echocardiography)</li></ul>
Septic Shock	<b>Severe sepsis PLUS</b> at least one of the following: <ul style="list-style-type: none"><li>• Systemic mean blood pressure&lt;60mmHg(&lt;80mmHg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg</li><li>• Need for dopamine &gt;5 µg/kg per minute or norepinephrine or epinephrine&lt;0.25µg/kg per minute to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)</li></ul>

Table 1. Definitions of diseases relevant to sepsis (adapted from Annane et al., 2005)

early diagnosis and early treatment are key to reducing morbidity and mortality in sepsis; and as such, it is advised to begin treatment while a diagnosis is being confirmed. In 2004, the first set of SSC guidelines was published, providing clinicians with an internationally recognized bedside tool for diagnosing and treating sepsis. In 2008, an

update to these guidelines was published, adding 33 new recommendations to the original 52 published in 2004 (Vincent, 2008). The updated recommendations were based on the results of a new method of assessing the quality of evidence and the strength of recommendations based on that evidence (Dellinger et al., 2008). The guidelines, however, are strictly guidelines, and as sepsis is so variable in etiology and presentation, these guidelines should not be seen to supersede the clinician's opinions or decisions when the entire patient's condition is taken into account.

## **2. Bundle treatment**

The idea of bundled care has found its place in the management of severe sepsis and septic shock. Bundles are evidence-based collections of interventions that result in more favorable outcomes when administered together rather than separately. In severe sepsis and septic shock, two bundles are recommended by the SSC – a Sepsis Resuscitation Bundle (containing five elements) and a Sepsis Management Bundle (containing four elements) the first of which are intended to be completed 100 percent within the first six hours of treatment and the second is to be completed within the first 24 hours (Severe Sepsis Bundles, n.d.). The aim of the SSC to reduce mortality by 25 percent by 2009 has not been achieved but initial publications suggest significant improvements in mortality with increasing bundle compliance (Severe Sepsis Bundles, n.d.; Levy et al., 2010).

### **2.1 Sepsis resuscitation bundle**

This bundle has 5 elements:

1. Measure Serum Lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic within 3 hours of Emergency Department (ED) admission and within 1 hour of non-ED admission
4. Treat hypotension and/or elevated lactate with fluids, and apply vasopressors for ongoing hypotension
5. Maintain adequate central venous pressure (CVP) and central venous oxygen saturation (ScvO<sub>2</sub>)

(Severe Sepsis Bundles, n.d.)

Each element is discussed in this chapter.

### **2.2 Sepsis management bundle**

This bundle has 4 elements:

1. Administer low-dose steroids for septic shock
2. Administer recombinant human activated protein C (rhAPC)
3. Maintain glucose control with a goal blood glucose approximating 150 mg/dl with a recommendation against intravenous insulin therapy titrated to keep blood glucose in the normal range (80-110 mg/dl) in patients with severe sepsis. Clinicians should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL
4. Maintain a median inspiratory plateau pressure (IPP) <30 cm H<sub>2</sub>O for mechanically ventilated patients

(Severe Sepsis Bundles, n.d.)

Each element is discussed in this chapter.

### 3. Primary management of sepsis

Morbidity and mortality can be greatly reduced with prompt recognition, diagnosis, and treatment of severe sepsis and septic shock (Dellinger et al., 2008; Sessler et al., 2004). There is strong evidence that will be further discussed in detail, indicating that the onset of treatment has a direct affect on the outcome of disease. The initial goals are to stabilize any respiratory dysfunction and then to promptly assess and address deficits in tissue and organ perfusion in order to avoid or minimize multiple organ damage.

#### 3.1 Stabilize respiration (mechanical ventilation)

As with any emergency, it is crucial to ensure there is sufficient respiration before addressing other issues. Oxygen should be administered early to patients with severe sepsis or septic shock, and it is often necessary to intubate and ventilate patients in the presence of significant CNS depression.

Investigations for acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) should be performed once respiratory stabilization is established. In patients with ALI or ARDS, it is suggested that positive end-expiratory pressure ventilation be used to prevent lung collapse at end-expiration although evidence from randomized controlled trials (RCTs) for this recommendation is lacking (Villar et al., 2006).

During mechanical ventilation of patients with ARDS, traditional tidal volume targets (10 ml per kilogram of body weight to 15 ml per kilogram of body weight) have been implicated in potential stretch-induced lung injury, while targeting low tidal volumes has been shown to prevent further injury to the lungs (Acute Respiratory Distress Syndrome Network, 2000). The Acute Respiratory Distress Syndrome Network coordinated a large multicenter trial indicating that low tidal volume mechanical ventilation used in the presence of acute lung injury reduced mortality rates from 39.8 percent in the standard tidal volume group to 31 percent in the low tidal volume mechanical ventilation group (relative reduction in mortality rate of 22.1 percent; 95 percent CI for the absolute difference between groups 2.4 percent to 15.3 percent) (Acute Respiratory Distress Syndrome Network, 2000). This trial involved randomly allocating patients with acute lung injury into one of two groups: low mechanical ventilation tidal volumes (6 ml per kilogram of predicted body weight) or standard mechanical ventilation tidal volumes (12 ml per kilogram of predicted body weight). In the low tidal volume group, plateau airway pressures measured at the end of inspiration were kept to  $\leq 30$  cm of water, whereas the standard tidal volume group, airway plateau pressures were restricted to  $\leq 50$  cm of water (Acute Respiratory Distress Syndrome Network, 2000).

#### 3.2 Assessment of perfusion

Hypoperfusion is a major contributing factor to the overall progression to multiple organ failure in septic shock (Casserly et al., 2009); therefore assessing perfusion is critical in management of severe sepsis and septic shock. Hypoperfusion often presents with cool extremities, oliguria, reduced pulse pressure, altered mental status, tachycardia, and high blood urea nitrogen to creatinine ratio; however these signs can be influenced by drugs and/or coincident disease, so their absence should not preclude perfusion assessment. In terms of assessment, blood pressure (BP) is a commonly used indicator of perfusion, however the sphygmomanometer has been shown to be potentially unreliable in hypotensive patients, and as such, arterial catheterization is recommended for assessment of perfusion (Hanna, 2003; Finnie et al., 1984; Cohn, 1967).



### 3.3 Restoration of perfusion

The inflammatory response associated with severe sepsis and septic shock is characterized by increased capillary permeability (resulting in leakage of plasma into the interstitial space) and decreased vasomotor tone, leading to decreased venous return to the heart (Snell and Parrillo, 1991) and ultimately a decreased cardiac output (Parrillo, 1993; Barochia et al., 2010). The consequence is hypoperfusion of organs and tissues. Typically, there is a sympathetic response – inducing tachycardia and increased arterial vasomotor tone; however, in severe sepsis and septic shock, there is often an attenuated vascular response (Parrillo, 1993). Since organ dysfunction or failure resulting from hypoperfusion is a major contributor to morbidity and mortality in severe sepsis and septic shock, prompt correction of hypoperfusion, once identified, is essential. The SSC guidelines “recommend... the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration  $\geq 4$  mmol/L)... as soon as [it] is recognized” (Dellinger et al., 2008).

#### 3.3.1 Central or mixed venous oxyhemoglobin saturation

Central or mixed venous oxyhemoglobin saturation (ScvO<sub>2</sub> and SvO<sub>2</sub>, respectively) can be used as a measure to gauge perfusion restoration. Low mixed venous oxyhemoglobin saturation has linked to undesirable outcomes in patients with septic shock (Edwards, 1991). In 2004, Reinhart et al conducted a prospective descriptive study during which they compared the values of central and mixed venous oxygen saturations in critically ill patients. Their results showed that ScvO<sub>2</sub> and ScO<sub>2</sub> paralleled each other quite reliably, with ScvO<sub>2</sub> measuring consistently about 7 saturation percent higher (Reinhart et al., 2004). Since SvO<sub>2</sub> measurement requires the insertion of a Swan-Ganz catheter it is therefore a more invasive measurement than ScvO<sub>2</sub>. Therefore the fact that, in most cases of severe sepsis, these values change in parallel is a welcome discovery (Bauer et al., 2008). The SSC guidelines recommend an ScvO<sub>2</sub> or ScO<sub>2</sub> of  $\geq 70$  percent or  $\geq 65$  percent, respectively (Dellinger et al., 2008). Additionally, they recommend targeting a mean arterial pressure (MAP) of  $\geq 65$  mm Hg and a urine output of  $\geq 0.5$  mL  $\text{kg}^{-1} \text{ hr}^{-1}$  (Dellinger et al., 2008).

In 2001, Rivers et al conducted a randomized controlled study of 263 patients to evaluate the efficacy, in terms of mortality reduction, of early goal-directed therapy (EGDT) administered prior to admission to the ICU. The aim of the study was to determine whether targeting a ScvO<sub>2</sub> or SvO<sub>2</sub> of  $\geq 70$  percent or  $\geq 65$  percent, respectively, in the first six hours post-admission would reduce mortality in patients presenting with severe sepsis and septic shock (Rivers et al., 2001). The results of this study showed a 30.5 percent in-hospital mortality in the early goal-directed therapy group as compared to an in-hospital mortality of 46.5 percent in the standard therapy group (Rivers et al., 2001), a 16 percent mortality reduction. In the time following the therapy up to three days post-presentation, the EGDT patients had a “higher mean (+/-SD) central venous oxygen saturation... lower lactate concentration... lower base deficit... and a higher pH” than the patients in the standard therapy group” (Rivers et al., 2001), indicating that the EGDT is significantly beneficial in the treatment of patients presenting with severe sepsis or septic shock.

As noted by Perel et al, many of the results obtained by Rivers et al, in their 2001 study, may not apply to patients in less severe sepsis. Perel states that “compared with other populations of septic patients, the patients of Rivers and colleagues had a higher incidence of severe comorbidities, a more severe hemodynamic status on admission (excessively low central venous oxygen saturation [ScvO<sub>2</sub>], low central venous pressure [CVP], and high lactate), and

higher mortality rates” (Perel, 2008). Also, in sepsis, it has been shown that SvO<sub>2</sub> may be raised even in the presence of tissue hypoxia. This implies that the ScvO<sub>2</sub> may sometimes be unreliable in targeted resuscitation (Perel, 2008; Bellomo et al., 2008). Another concern, proposed by Reinhart and Bloos, is the reversal of the physiologic difference between ScvO<sub>2</sub> and SvO<sub>2</sub> that can be observed in the state of cardiocirculatory shock resulting from reduced mesenteric blood flow followed by an increase of O<sub>2</sub> extraction in these organs. Consequently, this lowers venous saturation in the mesenteric circulation and, subsequently, the inferior vena cava. In healthy humans, the oxygen saturation in the inferior vena cava is higher than in the superior vena cava. But, in shock, when blood is diverted from the gut to other vital organs the oxygen saturation in the inferior vena may be substantially reduced. Since the pulmonary artery contains a mixture of blood from both the superior as well as the inferior vena cava, SvO<sub>2</sub> is normally greater than the oxygen saturation in the superior vena cava but this can be reversed during shock due to venous desaturation in the mesenteric circulation and the inferior vena cava (Reinhart and Bloos, 2005).

### 3.3.2 Lactic acid clearance

Using lactic acid clearance has been proposed as an alternative to measuring ScvO<sub>2</sub> and SvO<sub>2</sub> for assessing restoration of perfusion where ScvO<sub>2</sub>/SvO<sub>2</sub> monitoring may be unavailable; however, there is evidence that using both ScvO<sub>2</sub>/SvO<sub>2</sub> and lactic acid clearance may be appropriate (Arnold et al., 2009). During sepsis, tissue hypoxia causes an increase in cellular lactic acid production that diffuses into the blood (Arnold et al., 2009). It has been shown that a rise in lactic acid levels in the blood is associated with increased morbidity and mortality, and a decrease in blood lactic acid is associated with better, in patients with septic shock (Bakker et al., 1991).

A recent multicenter randomized non-inferiority study by Jones et al was conducted to evaluate whether using lactic acid clearance as an EGDT target was as efficacious as using ScvO<sub>2</sub>. This study looked at 300 patients, where one randomly selected group was administered EGDT targeting a lactic acid clearance of 10 percent and the other was given EGDT targeting an ScvO<sub>2</sub> of 70 percent (Jones et al., 2010). Both groups were resuscitated to normalize both CVP and MAP (Jones et al., 2010). The results showed the in-hospital mortality of the “ScvO<sub>2</sub>” group to be 23 % (95 % Confidence Interval [CI], 17 % - 30 %) and the “lactic acid clearance” group to be 17 percent (95 % CI, 11 % - 24 %) (Jones et al., 2010). This supported the non-inferiority hypothesis, as there was no significant difference in in-hospital mortality between the two groups.

In a 2004 prospective observational study by Nguyen et al, the clinical utility of lactic acid clearance was assessed. The researches observed the lactic acid clearance over the initial 6 hours of treatment and predicted that a high lactic acid clearance would correlate with higher in-hospital survival. They showed that “there was an approximately 11 percent decrease likelihood of mortality for each 10 percent increase in lactate clearance” (Nguyen et al., 2004).

A more recent study by Arnold et al investigated the association between early lactate clearance and severe sepsis patient survival (Arnold et al., 2009). Of the 166 patients, lactic acid non-clearance was evident in 15. The mortality rate for those 15 was 60 percent, whereas the mortality rate for the lactic acid clearance patients was 19 percent. Interestingly, this same study showed “discordance between ScvO<sub>2</sub> optimization and lactate clearance; 79 percent of lactate non-clearance had concomitant ScvO<sub>2</sub> of 70 percent or greater” (Arnold et al., 2009). They concluded that failing to clear lactic acid was associated with a high risk of death, and that attaining an ScvO<sub>2</sub> of 70 percent or greater did not rule out lactic acid non-

clearance, indicating that ScvO<sub>2</sub> optimization alone may not be a sufficient target to reduce mortality in the early stages of severe sepsis and septic shock (Arnold et al., 2009).

### 3.3.3 Central venous pressure (CVP)

Central venous pressure has long been used as a determinant of central venous blood volume or right ventricular preload in critically ill patients requiring hemodynamic monitoring. The validity of these correlations, however, has been brought to question. In 2004, Kumar et al conducted a prospective, nonrandomized, non-blinded interventional study evaluating the correlation between pulmonary artery occlusion pressure (Ppao) and left ventricular preload and between CVP and right ventricular preload; the results of this study indicate that “neither central venous pressure nor pulmonary artery occlusion pressure appears to be a useful predictor of ventricular preload with respect to optimizing cardiac performance” (Kumar et al., 2004). The SSC guidelines, however, still recommend targeting resuscitation to a CVP of 8-12mm Hg (Dellinger et al., 2008).

### 3.3.4 Intravenous fluids

Hypovolemia is a commonly present in systemic inflammation, and is defined as an insufficient blood plasma volume. It is associated with tachycardia, hypotension, and hypoperfusion, and can further complicate severe sepsis and septic shock. Early and aggressive fluid resuscitation has been shown to greatly reduce morbidity and mortality in sepsis, and the evidence produced by Rivers et al in 2001 indicates that the administration of approximately 1.5L more fluids than standard treatments in the first 6 hours may confer benefit in the form of reduction of morbidity or mortality (Rivers et al., 2001). It is recommended that specific goals and endpoints be set, treatment be titrated to these targets, and ongoing evaluations of the results be made by assessing perfusion (Hollenberg et al., 2004; Hollenberg, 2009). Worthy of note, is that CVP is not a good predictor of responsiveness to fluid resuscitation, and should not be used to guide treatment (Marik et al., 2008; Perel, 2008). Fluid resuscitation should be continued until hypotension and hypoperfusion are resolved, but should be discontinued or adjusted at the onset of pulmonary edema.

In term of the particular type of fluid used in resuscitation, a systematic review by Choi et al indicates that although resuscitation with crystalloids is associated with an overall lower mortality in trauma patients, there is no significant difference between crystalloid and colloid resuscitation in other patients (Choi et al., 1999). Also, in a multicenter, randomized, double blind trial comparing fluid resuscitation with albumin versus saline on patients in the ICU, Finfer et al found no difference in mortality (Finfer et al., 2004). In 2001, Wilkes and Navickis conducted a meta-analysis of randomized controlled trials to determine if human albumin administration was associated with increased mortality. Their findings were that there was no affect on mortality with the use of albumin, and therefor conclude that albumin use is safe (Wilkes et al., 2001). One recent multicenter two-by-two factorial trial evaluated the safety of pentastarch, a low-molecular-weight hydroxyethyl starch, in the fluid resuscitation of severe sepsis patients. Treatment of either pentastarch (a colloid) or Ringer’s lactate (a crystalloid) was given to patients as fluid for resuscitation. In the HES group, there was a higher incidence of renal failure and a higher rate of renal-replacement therapy than in the group resuscitate with Ringer’s lactate (Brunkhorst et al., 2008). So with the exception of pentastarch, it seems that thus far the choice of fluids, whether crystalloid



or colloid is insignificant as far as safety and efficacy is concerned, and as far as fluid resuscitation is concerned, early and aggressive treatment is the key to reducing morbidity and mortality in severe sepsis and septic shock.

3.3.5 Vasopressors

Occasionally, fluid resuscitation does not sufficiently reverse the hemodynamic and metabolic abnormalities associated with septic shock, and intravenous vasopressor therapy can be used to augment treatment effectively. When the MAP falls low enough, auto-regulation can fail causing tissues to rely strictly on pressure for perfusion (Dellinger et al., 2008). Maintaining a minimum MAP of 65 mmHg has been shown to provide sufficient tissue perfusion (LeDoux et al., 2000). Ideally, ‘fluid resuscitation’ alone is favorable over ‘fluid resuscitation plus vasopressor therapy’, so vasopressors should be utilized as second-line tools and used only when necessary. A true consensus has not been reached as to which specific vasopressor is most effective, and research into vasopressor therapy in severe sepsis and septic shock is ongoing (Hollenberg, 2009). As shown in Table 2, the various vasopressive agents have differing adrenergic affects (Schmidt, 2011b), and each case of severe sepsis or septic shock has its own characteristics, it is difficult to determine which drug is most appropriate (Myburgh et al., 2008); however, De Backer et al, in a recent multicenter randomized trial, showed that norepinephrine and dopamine were equivalent in reducing mortality in patients suffering from shock, but treatment with dopamine was associated with a significantly increased incidence of cardiac arrhythmias (De Backer et al., 2010), hypercalcemia, and decreased splanchnic circulation (Agrawal et al., 2010). Russell et al performed a multicenter randomized double-blind trial to determine the value of treatment with vasopressin in septic shock as compared to treatment with norepinephrine. The results indicated that there was no difference in the 28-day post-initiation mortality

Drug	Effect on Heart Rate	Effect on Contractility	Effects on Arterial Constriction
Dobutamine	+	+++	- (dilates)
Dopamine	++	++	++
Epinephrine	+++	+++	++
Norepinephrine	++	++	+++
Phenylephrine	0	0	+++
Amrinone	+	+++	-- (dilates)

Table 2. Vasopressors used in the treatment of septic shock (adapted from Schmidt, 2011b)

or the 90-day post-initiation mortality between the two groups (Russell et al., 2008). Also, there was no statistically significant difference in the incidence of adverse events (Russell et al., 2008). It is recommend in the SSC guidelines that the MAP is maintained at a minimum of 65 mmHg and either intravenous norepinephrine or intravenous dopamine be administered as the initial vasopressor to combat hypotension in patients with septic shock–with epinephrine being the first choice alternative vasopressive agent in patients who do not respond to norepinephrine or dopamine (Dellinger et al., 2008). In a recent animal study by Boyd et al, however, it was shown that treatment with vasopressin could decrease sepsis-induced pulmonary inflammation. They showed that with the intraperitoneal introduction

of lipopolysaccharide (LPS) there was consequent systemic and pulmonary inflammation – indicated by significant rises in both lung and serum interleukin-6 (IL-6; an inflammatory mediator) (Boyd et al., 2008). Two test groups were created – the test groups was treated with LPS and vasopressin, and the control group was treated with LPS and saline. With intraperitoneal LPS and vasopressin, the levels of both lung and serum IL-6 were reduced, whereas in the LPS and saline group, the LPS levels were raised as expected (Boyd et al., 2008). Pretreatment of the LPS and vasopressin group with V2R antagonists (agents which block the vasopressin receptor responsible for this protective effect) lead to similar rises in IL-6, as seen in the saline-treated mice (Boyd et al., 2008), indicating that vasopressin exerted its protective effects via the V2R receptor. These results suggest that vasopressin could have a potential future role as first line vasopressor in treating severe sepsis with acute lung injury.

### 3.3.6 Additional strategies

If all efforts with fluid resuscitation and vasopressor therapy fail to maintain a sufficient ScvO<sub>2</sub>, other strategies, such as inotrope therapy and transfusion of blood products, can be employed to attempt to reach acceptable pressure and perfusion targets. The SSC guidelines indicate that if the ScvO<sub>2</sub> has not reached  $\geq 70$  percent (65 percent for SvO<sub>2</sub>) with fluid resuscitation to the CVP target, they recommend the administration of a dobutamine infusion and/or the transfusion of packed red blood cells to achieve a hematocrit of  $\geq 30$  percent to reach an acceptable ScvO<sub>2</sub> or SvO<sub>2</sub> (Dellinger, 2008).

#### 3.3.6.1 Inotropes

Reserved for those patients not responding sufficiently to the above-mentioned interventions (attaining a ScvO<sub>2</sub> of  $\geq 70$  mmHg via fluid resuscitation and vasopressor therapy), inotropes can be used to increase the force of cardiac contraction and consequently increase cardiac output, blood pressure, and tissue and organ perfusion. Dobutamine is the recommended inotrope for patients in septic shock with coexistent myocardial dysfunction (Dellinger et al., 2008). Dobutamine is a drug that was developed by modifying the structure of isoproterenol, another inotrope, to reduce its chronotropic, arrhythmogenic, and vascular side effects while maintaining its inotropic effects (Tuttle and Mills, 1975). It is often used in cardiogenic shock, acting on  $\beta_1$  and  $\beta_2$  adrenergic receptors, but minimally on  $\alpha_1$  receptors. This profile accounts for its inotropic effects ( $\beta_1$  activity), its reduction of afterload ( $\beta_2$  activity), and its 'lack of vasoconstriction' or even 'mild vasodilation' effects (minimal  $\alpha_1$  activity) allowing it to enhance flow and the distribution of flow (Shoemaker et al., 1991). Occasionally, at low doses, dobutamine can cause a drop in blood pressure due to the vasodilation, however increasing cardiac output at higher dobutamine doses tends to override the drop in vascular resistance and blood pressure rises.

In a trial performed by Gattinoni et al, it was shown that targeting a cardiac index of supranormal levels did not confer a lower mortality rate among patients (Gattinoni et al., 1995), and therefore it is advised against pursuing such targets (Dellinger et al., 2008). Further supporting this recommendation are the results from a randomized trial performed by Hayes et al to determine whether dobutamine infusion, targeting a cardiac index greater than 4.5 liters per minute per square meter of body-surface area, an oxygen delivery rate above 600 ml per minute per square meter of body-surface area, and an oxygen consumption rate of above 170 ml per minute per square meter of body-surface area, would be associated with improved outcome for a group of critically ill patients (Hayes et al., 1994).

In this study, the results indicated that boosting the cardiac index and systemic oxygen delivery with a dobutamine infusion was, in some cases, actually detrimental to the patients, based on the in-hospital mortality rate being 34 percent in the control group and 54 percent in the treatment group (an absolute mortality increase of 20 percent) (Hayes et al., 1994).

### **3.3.6.2 Blood product transfusions**

There are conflicting data regarding the use of packed red blood cell transfusions used to raise the ScvO<sub>2</sub> in septic shock (Vincent et al., 2008; Rivers et al., 2001; Fuller et al., 2010). The SSC guidelines recommend treatment with packed red blood cell transfusion and/or intravenous dobutamine to treat patients whose ScvO<sub>2</sub> levels are inadequately responsive to fluid resuscitation and vasopressor therapy (Dellinger et al., 2008). This is based on the fact that the combination of fluid resuscitation, packed red blood cells, and intravenous dobutamine was associated with improved outcomes in severe sepsis and septic shock. It has been suggested, however, that the improved outcomes may be the result of the fluid resuscitation, dobutamine therapy, or other interventions included in the EGDT, and may have no link to the packed red blood cell transfusion itself.

In 2007, Sakr et al performed a prospective observational study to determine whether microvascular alterations participated in the development of multi-organ failure in severe sepsis. They set out to investigate the effect that red blood cell transfusions had on the microvascular perfusion of organs, using sublingual perfusion as their model. Their results showed that red blood cell transfusion had no significant effect on sublingual microcirculation in patients with severe sepsis, except for those with an altered baseline capillary perfusion (Sakr et al., 2007).

Recently, in a retrospective cohort study by Fuller et al, further evidence supports caution in the use of blood product transfusion in severe sepsis or septic shock. In this study, two groups were retrospectively compared – one treated with packed red blood cells and one treated without (Fuller et al., 2010). The pack red blood cell group produced a higher mortality (41.2 percent as compared to 33.9 percent in the group treated without red cells – an absolute mortality increase of 7.3 percent with red cell treatment) (Fuller et al., 2010). They also required more than double the mechanical ventilation days, more than double the hospital length of stay, and more than triple the ICU length of stay (Fuller et al., 2010).

## **4. Control of the septic focus**

SSC recommends properly obtaining at least two sets of blood cultures, from two different sites, drawn prior to beginning antimicrobial therapy in order to aid treatment and to narrow antibiotic coverage (Dellinger et al., 2004; Dellinger et al., 2008). Cultures should also be taken from any other potential source of infection including body fluids, tissues, and indwelling catheters.

### **4.1 Identification of the septic focus**

Cultures should be drawn prior to antimicrobial therapy so that to narrow antibiotic coverage and aid treatment. The SSC recommends proper identification of a pathogen, obtaining a least two sets of blood cultures from two different sites, as well as other potential source of infection (catheters, tissues, and body fluids). Patients presenting with severe sepsis should always be evaluated for the presence of a focus of infection, specifically the debridement of infected necrotic tissue, the drainage of an abscess or local focus of

infection, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination (Jimenez and Marshall, 2001).

4.2 Eradication of infection

Since the infection is the main triggering event of sepsis, early identification and successful eradication of the responsible organism should be a prime focus.

4.2.1 Source control

Built on an understanding of the biology of inflammation and the natural history of infectious processes, a clinician can provide an adequate set of management options. Source control includes physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area and quality of life. Table 3 illustrates many options for source control including debridement, drainage, device removal or more invasive steps. Studies supporting the various options for source control in reducing mortality would be difficult to conduct. Therefore, factors such as the current condition of the patient and past surgical and medical history should be taken into consideration when tailoring therapeutic and management options for source control to the individual patient (Houck et al., 2004). The present SSC guidelines recommend making a diagnosis in a septic patient requiring source control within six hours of presentation (Dellinger et al., 2008).

Source	Treatment
Sinusitis	Surgical decompression of the sinuses
Pneumonia	Chest physiotherapy, suctioning
Empyema thoracis	Drainage, decortication
Mediastinitis	Drainage, debridement, diversion
Peritonitis	Resection, repair, or diversion of ongoing sources of contamination, drainage of abscesses, debridement of necrotic tissue
Cholangitis	Bile duct decompression
Pancreatic infection	Drainage or debridement
Urinary tract	Drainage of abscesses, relief of obstruction, removal or changing of infected catheters
Catheter-related bacteremia	Removal of catheter
Endocarditis	Valve replacement
Septic arthritis	Joint drainage and debridement
Soft tissue infection	Debridement of necrotic tissue and drainage of discrete abscesses
Prosthetic device infection	Device removal

Table 3. Methods of source control for common ICU infections (adapted from Schmidt, 2011a)

4.2.2 Antimicrobial regimen

A retrospective study, of over 18,000 patient admitted with community acquired pneumonia, concluded that if antibiotics were given within 4 hours of arrival at the hospital, a significant reduction in in-hospital and 30 day mortality occurred (Houck et al., 2004). Another large multi-center retrospective cohort study reached the conclusion that in 2,731

patients with persistent or refractory hypotension, each hour of delay in the administration of appropriate antibiotics was associated with a 7.6 % mean decrease in survival. The same study found that if antibiotics were administered within 30 minutes of the first occurrence of hypotension, survival rate was 83 % but declined to 42 % when antibiotics were not administered until the sixth hour after first documentation of hypotension (Kumar et al., 2006). The relationship between the timing of administration of antibiotics, was further supported by Gaieski and colleagues who found that there was a 13.7 % decrease in mortality in 261 septic patients presenting to a single urban academic medical department, when appropriate antibiotics were given to septic patient within one hour of triage compared with more than 1 hour of triage (Gaieski et al., 2010; Zubert et al., 2010; Dellinger et al., 2008). Appropriate initial choice of antibiotic coverage is an independent predictor of survival in patients with sepsis. Gaieski and Colleagues, used a recent retrospective cohort study to demonstrate that patients who received appropriate antibiotics, as prescribed by an institution specific antibiotic nomogram, compared to those who did not receive appropriate antibiotics, had a reduction of 17.5 % in mortality rates (Gaieski et al., 2010; Zubert et al., 2010). Other studies found a significantly increased relative risk of death of 2.18 if patients originally received inadequate antibiotic coverage in the UCU for bloodstream infections (Ibrahim et al., 2000). Another challenge to the appropriate and well-times administration of antimicrobial is the increasing drug resistant pathogens. In a 760 patients retrospective study, Micek et al found that patients who received initial combination therapy involving gram-negative bacteria had a significantly lower rates (36 %) as opposed to patients that did not (52 %) (Micek et al., 2010). Almost all evidence for timely and appropriate antibiotic use stem from cohort studies, it is therefore possible that the relationship with regards to mortality, timely and appropriate antibiotics management might be indirect and represent a surrogate marker for other components of quality care. The SSC recommends timely and appropriate empiric antibiotic therapy that has known susceptibility for all possible pathogens (Dellinger et al., 2008).

## 5. Additional therapies

Based on the personalized needs of the patient, several additional therapies, when appropriate, are considered for the management and treatment of a septic patient. These include therapies such as recombinant human activated protein C, steroids, nutrition and intensive insulin therapy. Strong evidence, discussed below, show benefits in improving patient outcomes and quality of life.

### 5.1 Recombinant human activated protein C (rhAPC)

Administration of Recombinant Human activated Protein C (rhAPC) has been linked to a significant reduction in mortality in patients with a relatively high likelihood of death (Fourrier, 2004). Produced by the liver and activated in the circulation, Protein C acts by cleavage and inhibition of factors Va and VIIIa therefore functioning as a natural anticoagulant. Activated protein C (APC) plays an essential role in inflammation by inhibiting thrombin generation and maintaining the permeability of blood vessel walls. Conversely, endogenous levels of activated protein C are markedly reduced in sepsis and are associated with poor outcome (Shorr et al., 2006; He et al., 2007; Fisher and Yan, 2000). The PROWESS study, where 1690 patients with severe sepsis were randomized to rhAPC infusion for 96 hours or placebo had to be aborted early for efficacy after an absolute risk reduction of death of 6.1 percent with the administration of rhAPC was demonstrated



(Bernard et al., 2001). Later sub-group analysis of the PROWESS study found that the highest reduction in mortality rate with the administration of rhAPC was in patients with multi-system organ failure or very high risk of death defined by Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25 or greater (Beutler, 2004). Another safety study (ENHANCE) found a very similar reduction in mortality rate and that administration within the first twenty-four hours was indeed associated with a higher reduction in mortality (Levy et al., 2005). ADDRESS, another open-label safety study of 2640 patient with sepsis and a low risk of death were randomized to rhAPC or placebo. It was concluded that there were no reduction in mortality in patients with severe sepsis with a low likelihood of death (Abraham et al., 2005). A non-randomized propensity-matched analysis of 33,749 patients with severe sepsis, found a significant reduction in hospital mortality with the administration of rhAPC (Lindenauer et al., 2010). These findings led to the current recommendation from the SSC guidelines to use rhAPC for patients with sepsis with high risk of death if there are no contraindications (Dellinger et al., 2008). Although these are still the current SSC guidelines, recombinant human activated protein C has recently been withdrawn from the market due to lack of efficacy.

## 5.2 Steroids

Adrenal insufficiency is a common feature of sepsis. Adrenal dysfunction is found in about 30 percent of all critically ill patients, and this percentage rises to 50 to 60 percent in septic shock (Annane and Bellissant, 2000). The presence of adrenal insufficiency in septic shock patient has been associated with higher mortality rates (Annane and Bellissant, 2000). Nevertheless, the benefit of administering exogenous steroids in septic shock remains a controversy. Good evidence has shown that administration of high dose corticosteroids (>300 mg hydrocortisone per day) has no mortality benefit and in fact might even lead to increased mortality (Bone et al., 1987; Minneci et al., 2004). The utility of low dose corticosteroid in reducing mortality is however less controversial (<300 mg hydrocortisone per day). Annane and colleagues randomized 300 septic patients in 19 French ICUs unresponsive to vasopressor therapy with a positive cosytropin stimulation test to low-dose hydrocortisone and fludrocotisone or placebo. They concluded that patients initially unresponsive to vasopressors with a positive cosytropin stimulation test randomized to low-dose hydrocortisone and fludrocotisone had a significantly lower mortality rate (Annane et al., 2002). According to the Corticosteroid Therapy for Septic Shock (CORTICUS) study, a subsequent multi-country trial of 499 patients showed no reduction in mortality in the group that received hydrocortisone compared to placebo. It is difficult to compare these two trials as the CORTICUS study included patients with septic shock irrespective of whether their blood pressure responded initially to vasopressors (Sprung et al., 2008). A recent randomized control trial found that adding fludrocotisone, when hydrocortisone is administered to patients with severe sepsis, showed no improvement in in-hospital mortality (Annane and Bellissant, 2000). Similarly, two recent systematic reviews found no overall survival benefit by administering low dose steroids (Annane et al., 2009; Sligl et al., 2009). The current SSC guidelines recommend using low dose hydrocortisone only when there is a poor initial response to vasopressors (Dellinger et al., 2008).

## 5.3 Nutrition

The primary aim of nutritional support is to supply the substrates essential to meet the metabolic needs of critically ill patients. The acute phase is characterized by catabolism

exceeding anabolism where carbohydrates are used as the preferred energy source, since fat mobilization is impaired. Nutritional support would provide the necessary carbohydrates to meet this demand and therefore alleviate the usual metabolic response of an inflammatory state to break down muscle proteins into amino acids that will eventually serve as a substrate of gluconeogenesis. The recovery phase would shift the dominant response towards anabolism, in which the body corrects the hypoproteinemia, replenishes other nutritional stores, and repairs muscle loss (Dvir et al., 2006). Conflicting data with regards to route of delivery exist. Enteral nutrition, compared with parenteral nutrition, results in poorer achievement of nutritional goals but may be associated with fewer infections.

The mechanisms by which enteral nutrition decreases infectious complications are unknown. However, preservation of gut immune function and reduction of inflammation have been proposed (Alverdy et al., 2003; Clave and Heyland, 2009). It is uncertain whether nutritional support directly improves important clinical outcomes (e.g. duration of mechanical ventilation, length of stay, mortality), or when nutritional support should be initiated.

The goal of nutrition support has been to deliver 100% of nutrient requirements, calculated for the specific metabolic condition, and in the shortest time possible. Recently, clinical experts in intensive care medicine and nutrition, published studies that determined that for critically ill patients, administering nutrients at quantities less than the calculated metabolic expenditure may significantly improve outcomes (Dickerson et al., 2002). Conversely, in a prospective cohort study from Johns Hopkins Medical Center, ICU patients were divided into groups that received 0%-32% (group one) of recommended intake, groups that received 33%-65% (group two) and groups that received 66%-100% (group three) of caloric recommendations. Patients in group two showed the highest survival rate and experienced more sepsis free days as opposed to patients in group three who experienced the worst outcomes (Dickerson et al., 2002). In another retrospective analysis of obese critically ill patients, Dickerson et al. reported that patients receiving less than 20 kcal/kg adjusted weight/day compared with patients receiving greater than 20 kcal/kg adjusted weight/day experienced fewer days in the ICU, fewer days on mechanical ventilation, and fewer days of antibiotic use (Krishnan et al., 2003). However, definitive evidence for the optimal amount of nutritional support and the mode of delivery has yet to be determined in severe sepsis.

#### **5.4 Intensive insulin therapy**

Tight glucose control has showed early hopes of reducing mortality of critically ill patients. Indeed, Van den Berghe and colleagues studied 1548 cardiac surgery ICU patients who were randomized either to very tight glucose control (80-110mg per deciliter) through intensive insulin therapy (IIT) or to conventional treatment (280 to 200 mg per deciliter) (Van Den Berghe et al., 2001). The study showed a significant 3.4 percent absolute mortality reduction among all patients and a 9.6 percent absolute risk reduction in mortality for patients who remained in the ICU for greater than five days. However, the same authors showed that there was no reduction in mortality when the same procedure was applied in a medical ICU (Van den Berghe et al., 2006). Furthermore, accumulation of evidence through out recent years from RCTs show that tight glucose control in non-surgical ICU has no significant correlation in mortality benefit and could, in fact, be harmful. A meta-analysis of 29 randomized controlled trials involving 8432 patients found no reduction in mortality with IIT compared to standard treatment (Wiener et al., 2008). In one study, involving 532

patients with severe sepsis randomized to IIT or conventional insulin therapy (180 to 200 mg per deciliter) and various combinations of crystalloids or colloids, showed no difference in mortality with IIT or conventional therapy but a significant increase in severe hypoglycemia in the IIT group. The study had to be stopped earlier than predicted due to increased significant hypoglycemic events in the IIT group (Brunkhorst et al., 2008). The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study randomized 6104 medical and surgical patients within 24 hours of ICU admission to IIT or conventional therapy (180 mg per deciliter or less). A significant increased risk of death (odds ratio 1.14) was shown in both medical and surgical group of patients who received IIT. (Finfer et al., 2009). Current SSC guidelines recommend a glucose target of <180 mg/dl for patients with severe sepsis and septic shock (Dellinger et al., 2008).

## 6. Summary of SSC recommendations

The 2008 Surviving Sepsis Campaign Guidelines (Dellinger et al., 2008) contain 3 tables that are very useful in summarizing their recommendations for the management of severe sepsis and septic shock. The following recommendations are adapted from those three tables with the very kind permission of Dr. Phil Dellinger (chair of 2008 Surviving Sepsis Campaign Committee).

### 6.1 Initial resuscitation and infection issues (Dellinger, 2008)

Regular text represents “Strongly Recommended” and *italicized* text represents “Suggested”.

#### 6.1.1 Initial resuscitation (first 6 hours)

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission
- Resuscitation goals
  - CVP 8–12 mm Hg (A higher target CVP of 12–15 mm Hg is recommended in the presence of mechanical ventilation or preexisting decreased ventricular compliance.)
  - Mean arterial pressure  $\geq 65$  mm Hg
  - Urine output  $\geq 0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$
  - Central venous (superior vena cava) oxygen saturation  $\geq 70$  percent or mixed venous  $\geq 65$  percent
- *If venous oxygen saturation target is not achieved*
  - *Consider further fluid Transfuse packed red blood cells if required to hematocrit of  $\geq 30$  percent and/or*
  - *Start dobutamine infusion, maximum  $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$*

#### 6.1.2 Diagnosis

- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration
  - *Obtain two or more blood cultures*
  - *One or more blood cultures should be percutaneous*
  - *One blood culture from each vascular access device in place >48 hours*
  - *Culture other sites as clinically indicated*

- Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so

### 6.1.3 Antibiotic therapy

- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis and septic shock
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs
- *Consider combination therapy in Pseudomonas infections*
- *Consider combination empiric therapy in neutropenic patients*
- *Combination therapy  $\leq 3-5$  days and de-escalation following susceptibilities*
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies
- Stop antimicrobial therapy if cause is found to be noninfectious

### 6.1.4 Source identification and control

- A specific anatomic site of infection should be established as rapidly as possible and within first 6 hours of presentation
- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement)
- Implement source control measures as soon as possible following successful initial resuscitation (exception: infected pancreatic necrosis, where surgical intervention is best delayed)
- Choose source control measure with maximum efficacy and minimal physiologic upset
- Remove intravascular access devices if potentially infected

## 6.2 Hemodynamic support and adjunctive therapy (Dellinger, 2008)

Regular text represents “Strongly Recommended” and *italicized* text represents “Suggested”.

### 6.2.1 Fluid therapy

- Fluid-resuscitate using crystalloids or colloids
- Target a CVP of  $\geq 8$  mm Hg ( $\geq 12$  mm Hg if mechanically ventilated)
- Use a fluid challenge technique while associated with a hemodynamic improvement
- Give fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 minutes. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement

### 6.2.2 Vasopressors

- Maintain MAP  $\geq 65$  mm Hg
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice

- *Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin 0.03 units/minute may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone*
- *Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine.*
- Do not use low-dose dopamine for renal protection
- In patients requiring vasopressors, insert an arterial catheter as soon as practical

### 6.2.3 Inotropic therapy

- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output
- Do not increase cardiac index to predetermined supranormal levels

### 6.2.4 Steroids

- *Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors*
- *ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone*
- *Hydrocortisone is preferred to dexamethasone*
- *Fludrocortisone (50 µg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used*
- *Steroid therapy may be weaned once vasopressors are no longer required*
- Hydrocortisone dose should be ≤300 mg/day
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it

### 6.2.5 Recombinant human activated protein C (rhAPC)

- *Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications.*
- Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC

## 6.3 Other supportive therapy of severe sepsis (Dellinger, 2008)

Regular text represents "Strongly Recommended" and *italicized* text represents "Suggested".

### 6.3.1 Blood product administration

- Give red blood cells when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin concentration of 7.0–9.0 g/dL in adults. A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis)
- Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons
- *Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures*



- Do not use antithrombin therapy
- Administer platelets when
  - Counts are  $<5,000/\text{mm}^3$  ( $5 \cdot 10^9/\text{L}$ ) regardless of bleeding
  - Counts are  $5,000\text{--}30,000/\text{mm}^3$  ( $5\text{--}30 \cdot 10^9/\text{L}$ ) and there is significant bleeding risk
  - Higher platelet counts ( $\geq 50,000/\text{mm}^3$  [ $50 \cdot 10^9/\text{L}$ ]) are required for surgery or invasive procedures

### 6.3.2 Mechanical ventilation of sepsis-induced ALI/ARDS

- Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS
- Target an initial upper limit plateau pressure  $\leq 30$  cm H<sub>2</sub>O. Consider chest wall compliance when assessing plateau pressure
- Allow PaCO<sub>2</sub> to increase above normal, if needed, to minimize plateau pressures and tidal volumes
- Set PEEP to avoid extensive lung collapse at end-expiration
- Consider using the prone position for ARDS patients requiring potentially injurious levels of FIO<sub>2</sub> or plateau pressure, provided they are not put at risk from positional changes
- Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated, between 30° and 45°
- Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild to moderate hypoxemic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly
- Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation
  - SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H<sub>2</sub>O or a T piece
  - Before the SBT, patients should:
    - Be arousable
    - Be hemodynamically stable without vasopressors
    - Have no new potentially serious conditions
    - Have low ventilatory and end-expiratory pressure requirement
    - Require FIO<sub>2</sub> levels that can be safely delivered with a face mask or nasal cannula
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion

### 6.3.3 Sedation, analgesia, and neuromuscular blockade in sepsis

- Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients
- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-titrate if necessary
  - Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions

#### 6.3.4 Glucose control

- Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU
- *Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment*
- Provide a glucose calorie source and monitor blood glucose values every 1–2 hours (4 hours when stable) in patients receiving intravenous insulin
- Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values

#### 6.3.5 Renal replacement

- *Intermittent hemodialysis and CVVH are considered equivalent*
- *CVVH offers easier management in hemodynamically unstable patients*

#### 6.3.6 Bicarbonate therapy

- Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH  $\geq 7.15$

#### 6.3.7 Deep vein thrombosis prophylaxis

- Use either low-dose unfractionated heparin (UFH) or low molecular weight heparin (LMWH), unless contraindicated
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated
- *Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis*
- *In patients at very high risk, LMWH should be used rather than UFH*

#### 6.3.8 Stress ulcer prophylaxis

- Provide stress ulcer prophylaxis using H<sub>2</sub> blocker or proton pump inhibitor. Benefits of prevention of upper gastrointestinal bleed must be weighed against the potential for development of ventilator-acquired pneumonia

#### 6.3.9 Consideration for limitation of support

- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations

### 7. Novel and ongoing research

Severe sepsis and septic shock management is an evolving and still controversial subject. New research is ongoing, and various therapies are being proposed and investigated.

#### 7.1 Recombinant Human Milk Fat Globule Epidermal Growth Factor 8 (rhMFG-E8)

A U.S. study is currently underway, and set for completion in on August 31<sup>st</sup>, 2012, investigating the benefits of rhMFG-E8 on the clearance of apoptotic cells in severe sepsis and septic shock. Apoptosis is an important any player in the pathobiology of sepsis, and the

lack of clearance of apoptotic cells is partially responsible for some of the pathology. The basis of this study is that in a rat model, they demonstrated that down-regulating the MFG-E8 gene expression was associated with reduced apoptotic cell clearance during sepsis. The MFG-E8 protein acts as an opsonin, targeting apoptotic cells phagocytosis, and without this opsonization, proper cell clearance does not occur. They have created recombinant human MFG-E8 and propose to use it as an adjunctive treatment for sepsis with the goal of improving cardiovascular function, attenuating tissue injury and inflammation, and reducing mortality (2011a).

### **7.2 Magnesium sulphate does not improve microcirculatory alterations**

It is well known that microcirculatory dysfunction is contributory to the pathology associated with severe sepsis and septic shock. Since magnesium sulphate has both endothelium-dependent and non-endothelium-dependent vasodilatory pathways, it has been proposed as a potential therapy for sepsis. Andrius et al conducted a single center open label clinical trial to assess the microcirculatory changes induced by infusion of magnesium sulphate. This trial failed to demonstrate any microcirculatory improvement with magnesium sulphate infusion (Pranskunas et al., 2011).

### **7.3 Targeting CCR2: A novel therapeutic strategy for septic shock**

Since sepsis is an inflammation-mediated disease, and neutrophils are among the first cells recruited in the inflammatory process, Souto et al proposed that hyper-activation of neutrophils may contribute to tissue damage in sepsis. They studied the role of the chemokine receptor CCR2 in inappropriate neutrophil recruitment and tissue damage in remote organs of septic patients. CCR2 is a receptor for a chemotactic factor 'monocyte chemoattractant protein-1' (CCR2 chemokine (C-C motif) receptor 2 [ Homo sapiens ], 2011b). The receptor-ligand interaction mediates monocyte chemotaxis and monocyte infiltration in inflammation. In this study, the expression and responsiveness of CCR2 was induced in circulating neutrophils during induced sepsis in mice(Souto et al., 2011). Mortality was prevented in both genetically and pharmacologically CCR2-inhibited mice. Neutrophil infiltration into the lungs, heart, and kidneys was reduced in both models, and serum biochemical markers of organ injury and dysfunction were also reduced (Souto et al., 2011). These results implicate CCR2 as a potential target for antagonist pharmaceutical therapy in severe sepsis and septic shock to prevent 'multiple organ dysfunction syndrome'.

### **7.4 Targeting LPS to impair induction of inflammation**

Lipopolysaccharide (LPS), a surface molecule of gram-negative bacteria, interacts with the Toll-like receptor 4 (TLR-4) in the induction of the inflammatory response, and the associated signal transduction pathway has been associated with the pathogenesis of sepsis. Neutralizing LPS before it can interact with TLR-4 has been proposed as an adjunctive therapy for sepsis (Wheeler et al., 2009). Lipid-binding protein (LBP) is a molecule that directs LPS to the TLR-4 receptor (Wheeler et al., 2009). Analogues of this molecule can block LPS-LBP interactions and inhibit LPS-induced inflammation. This may prove to be a promising novel therapy for sepsis.

## **8. Conclusion**

It is evident that there is a great deal of research still needed to resolve many of the controversies around the management of sepsis and to discover the best management

strategies for severe sepsis and septic shock. Sepsis management recommendations are clearly improving with each study performed, and efforts towards the standardization and universalization of protocols, is a great step in the right direction. The 2008 Surviving Sepsis Campaign guidelines are, pending an update, the most up-to-date complete set of evidence-based guidelines on the management of severe sepsis and septic shock that we have found.

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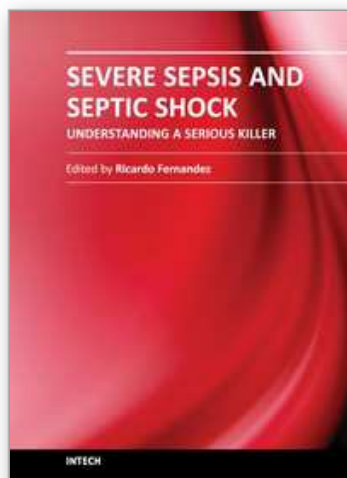


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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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