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The Hospital Physician Critical Care Medicine Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in critical care medicine. Each manual reviews a topic essential to the current practice of critical care medicine.

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Cover Illustration by Kathryn K. Johnson

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Critical Care Medicine  Volume 8, Parts 4

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Severe sepsis and septic shock affect over 750,000 people in the United States each year, resulting in over 200,000 deaths. Recent work by Martin and colleagues indicates that the incidence of sepsis is increasing; however, the overall case fatality rate may be decreasing. With the ageing population in the United States, the incidence of sepsis is expected to continue to rise. This monograph discusses current definitions of sepsis, reviews key components of the pathophysiology of sepsis, and presents an organized approach to management of severe sepsis and septic shock.

Sepsis begins with an insult that sets off an inflammatory response. This response may progress through a continuum which, at worst, may culminate in multisystem organ dysfunction and death. Definitions of conditions comprising the sepsis continuum were proposed by Bone and colleagues in 1992. While the definitions help provide an organized understanding of the continuum of sepsis, certain limitations do exist. In general, the definitions may be overly sensitive and non-specific. In addition, several of the defined states may be subject to interpretative variability, such as the concept of septic shock being defined as “hypotension despite adequate fluid resuscitation.” Physicians may differ considerably on how they define “adequate fluid resuscitation.” Thus, a patient may be placed on vasopressors after 1 to 2 L of fluid (ie, septic shock) under the care of one physician, whereas a second physician may choose to administer 5 to 6 L of fluid to the same patient and never initiate vasopressor support (ie, severe sepsis). Therefore, the definition of septic shock may reflect the treatment pathway taken by a physician rather than the physiology of a patient. Additionally, a strict definition of shock based on blood pressure fails to acknowledge that severe tissue hypoperfusion may exist in the presence of adequate pressure. Despite these limitations, the definitions are widely utilized in the clinical arena and particularly in research. While change may occur in the future, Rangel-Frausto and colleagues in part, validated the continuum of the definitions by showing a general incremental increase in mortality with progressive disease (Figure).

Sepsis encompasses a complex inflammatory reaction to infection that includes derangements in coagulation, immune function, endothelial function, and tissue oxygenation. Sepsis begins with a source of infection that leads to a generalized and oftentimes exaggerated inflammatory response. In approximately 25% of cases, cultures may be negative and a source of infection is not readily identifiable. Nevertheless, cellular components of whatever pathogens are present cause monocytes, neutrophils, and macrophages to generate cytokines and other immune mediators that activate the complement system and promote neutrophil activity against the pathogen. Foremost of the cytokines are the interleukins, particularly the interleukin (IL)-1 family and tumor necrosis factor-α (TNF-α). Other mediators include arachidonic acid metabolites, HMGB-1, and platelet-activating factor.

In certain instances, activation of inflammatory mediators can be profound and may correlate directly with mortality. Elevated TNF-α in sepsis caused by Neisseria meningitides infection is an example of a cytokine-disease interaction that significantly correlates with mortality. However, pinpointing specific cytokine elevations as being causative of end-organ damage is typically not possible, and markedly elevated measurable levels of specific cytokines are the exception rather than the norm. Several studies have noted that only 10% to 20% of patients have detectable elevated levels of TNF-α or IL-1. To that end, efforts to pharmacologically block TNF-α have generally failed to improve mortality in the majority of patients with severe sepsis.

The cardiovascular and endothelial effects of immune mediators may become detrimental to tissue oxygen delivery in severe sepsis. TNF-α and IL-1 are associated with increased nitric oxide levels that cause vasodilation and myocardial suppression. Mediators such as complement and bradykinin cause systemic vasodilation, hyperemia, and increased endothelial permeability. Polymorphonuclear leukocytes directly contribute by releasing reactive oxygen species, other vaso-dilatory agents, and proteolytic enzymes in the
Systemic Inflammatory Response Syndrome (SIRS). The systemic inflammatory response to a wide variety of severe clinical insults, manifested by 2 or more of the following conditions:
- Temperature > 38°C or < 36°C
- Heart rate > 90 bpm
- Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg
- Leukocyte count > 12,000/mm³ or < 4000/mm³, or > 10% immature (band) forms

Sepsis. The systemic inflammatory response to infection. The diagnosis of sepsis requires the presence of at least 2 SIRS criteria plus an infection. Signs of infection include an inflammatory response to the presence of microorganisms or the invasion of a normally sterile host tissue by those organisms.

Severe sepsis (SIRS). Sepsis (SIRS) associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Sepsis inducible hypotension. A systolic blood pressure < 90 mm Hg or a reduction of ≥ 40 mm Hg from baseline in the absence of other causes for hypotension.

Septic shock (SIRS shock). A subset of severe sepsis with hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock (SIRS) shock. A subset of severe sepsis with hypotension despite adequate fluid resuscitation along with presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic (SIRS) shock.

Multiple organ dysfunction syndrome (MODS). Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.


ACCP = American College of Chest Physicians; SCCM = Society of Critical Care Medicine.

Microcirculation. The result of these microcirculatory changes is diminished oxygen diffusion to cells that have higher metabolic demand. These cardiovascular effects are compounded by suppression of the hypothalamic–pituitary–adrenal axis in severe sepsis.

Direct hypothalamic and pituitary inhibition leads to diminished release of cortisol by the adrenals relative to the shocked state. Vasopressin levels in severe sepsis, while oftentimes initially elevated, may become diminished as disease progresses.

Cytokine activity in sepsis tips the balance between coagulation and fibrinolysis towards coagulation. Cytokine activity promotes coagulation through activation of the extrinsic pathway, and TNF-α is one cytokine primarily implicated in promoting this activation. Bacterial lipopolysaccharide also causes direct activation of the coagulation cascade. Also, early activation of the fibrinolytic system may be replaced by later suppression of this pathway. This suppression is affected in part by diminished conversion of protein C to activated protein C, which inhibits factors Va and VIIIa. The result of the deregulation of the coagulation and fibrinolytic systems is microcirculatory fibrin deposition in end organs that further contributes to increased inflammation and diminished oxygen delivery.

Sepsis-induced immunosuppression is inadequately understood but likely is an important sequelae of prolonged severe sepsis. A degree of anti-inflammatory response mediated by type 2 helper T cells is necessary to counter-regulate the immune system’s inflammatory response to infection. Nevertheless, this type 2 helper T cell response can become too pronounced, at the expense of adequate host defense. Inflammatory mediators can markedly depress granulocyte formation. A recently proposed hypothesis for the failure of the host defenses is apoptosis of lymphocytes. Sepsis induces apoptosis of T cells, B cells, and dendrites. Moreover, the apoptotic death of these cells leads to anergy. This form of cell death has the opposite effect of necrotic death, which further stimulates the immune system. Autopsy studies have confirmed the measurable loss of B cells, T cells, and dendritic cells in patients who have died from sepsis.

**PRINCIPLES OF SEPTIC SHOCK MANAGEMENT**

Management principles for septic shock include the following components: early recognition, early and adequate antibiotic therapy, source control, early hemodynamic resuscitation and continued support, administration of corticosteroids (refractory vasopressor-dependent shock) and drotrecogin alfa (in severely ill patients—APACHE II > 25), tight glycemic control, and proper ventilator management with low tidal volume in patients with acute respiratory distress syndrome (ARDS).
EARLY RECOGNITION

Early identification of sepsis likely results in improved outcome.9 While overt septic shock may be easy to recognize, sepsis (and ultimately septic shock) can present in a variety of ways, and a high level of suspicion is needed to identify subtle presentations. Many indicators of sepsis, such as fever, leukocyte count, tachycardia, and tachypnea, have poor sensitivity and poor specificity.10 For example, fever is considered an indicator of sepsis, although a septic patient may be hypothermic, hyperthermic, or even normothermic.

After proper identification of a septic patient, care must be taken to recognize signs of tissue hypoperfusion. Blood pressure does not necessarily reflect the degree of tissue perfusion.11 A hypertensive or normotensive patient may have inadequate tissue perfusion, whereas a patient with a “low pressure” may still maintain adequate perfusion. For example, a patient with chronic cirrhosis may, in a normal physiologic state, maintain a blood pressure of 90/60 mm Hg and have adequate perfusion. In contrast, a poorly compliant hypertensive patient with a blood pressure of 120/80 mm Hg may be “hypotensive” and/or hypoperfused. In addition, a patient may be in a state of compensated shock in which decreased blood pressure is a late indicator of the extent of disease. Thus, other signs of tissue hypoperfusion must be sought.

On physical examination, signs of tissue hypoperfusion include cool and/or clammy extremities and mottling. A shock index greater than 0.9 (calculated by dividing heart rate by systolic blood pressure) may also be indicative of hypoperfusion in a patient with “normal” blood pressure.12,13 Finally, metabolic indices such as lactic acidosis, base deficit, and bicarbonate concentration should be measured to help determine perfusion status.9,14,15 Lactic acid levels greater than 4 mmol/dL were used to screen for tissue hypoperfusion in the Early Goal-Directed Therapy (EGDT) trial.9 Shapiro and colleagues14 recently found that lactic acid levels greater than 4 mmol/dL were associated with increased mortality, thus validating this cut-off point. Patients with evidence of tissue hypoperfusion should be properly identified and treated appropriately (see Hemodynamic Support/Resuscitation).

SOURCE CONTROL

Early identification and eradication of the source of sepsis is essential for proper management (Table 2). Abdominal sources of sepsis should be identified and early surgical consultation should be obtained. Abscesses must be drained in almost all scenarios, and indwelling catheters (eg, renal dialysis lines) must be removed. While this concept of finding and eradicating the source is seemingly basic and logical, randomized trials in this area are difficult, and this limitation results in lower levels (grade E) of recommendations from evidence-based reviews.16–18 The optimal timing for intervention may depend on the source of sepsis and the status of the patient. In general, early eradication of the source is preferred, but this is not always possible. For example, in a hemodynamically unstable patient, a dialysis catheter can be quickly removed, but a major operative procedure may need to be preceded by aggressive administration of fluids in order to achieve the optimal outcome.

EARLY ANTIBIOTICS

While common sense suggests that early administration of adequate antibiotics would result in improved outcome, this hypothesis has only recently been shown...
to be accurate. Thus, early in the course of disease, empiric broad-spectrum antibiotics are warranted, and the concept of “waiting until the results of cultures are back” is not a valid reason to withhold antibiotics. The Surviving Sepsis Campaign recommends a goal of administering antibiotics within 1 hour of identifying sepsis. When culture results are available later in the course of disease, the antibiotic regimen can be tailored to the isolated organism. When de-escalation or discontinuation of antibiotics occurs, limitations of source identification must be taken into account. In large sepsis cohort studies, the rate of positive blood cultures typically is approximately 30%. Another 40% of patients will have a positive culture from a specific site but will have negative blood cultures (eg, urinary tract infection, abscess). The remaining 25% of patients remain culture-negative yet may display mortality rates similar to their culture-positive counterparts. Thus, many culture-negative patients may have infection that has not been identified for several reasons (eg, because antibiotics were delivered prior to blood culture or inadequate volumes of blood were collected).

HEMODYNAMIC SUPPORT/RESUSCITATION

Proper hemodynamic resuscitation and support are essential to achieving reversal of the shock state. Natanson et al demonstrated the importance of resuscitation/support and administration of antibiotics in the septic patient using an animal model. He divided septic dogs (method utilized was an infected peritoneal clot) into 4 groups: dogs without any therapy, those receiving only antibiotics, those receiving only hemodynamic support, and those receiving both hemodynamic and antibiotic support. As expected, the group without therapy had a 100% mortality rate. Both the antibiotic group and hemodynamic groups independently had an 87% mortality, whereas the combination of antibiotics and hemodynamic support resulted in the optimal outcome (57% mortality).

Likewise, human trials of early septic and septic-like (ie, systemic inflammatory response syndrome [SIRS]) states concluded that aggressive hemodynamic support improves outcome. According to the EGDT trial, 263 patients were randomized to either a control group or a therapy arm. Patients in the therapy arm received aggressive resuscitation via maximization of preload (central venous pressure to 8 to 12 mm Hg), afterload (vasopressors/vasodilators to keep mean arterial pressure between 65 and 90 mm Hg), and contractility (dobutamine for central venous oxygen saturation [ScvO2] < 70% after transfusion to hematocrit > 30%). A 16% improvement in mortality was reported for this treatment strategy.

Oxygen Delivery

The provision of hemodynamic support essentially translates to restoring perfusion to the shocked patient. In the shocked state, tissue demand exceeds tissue supply and hypoperfusion of tissues occurs. The components of oxygen delivery (DO2) consist of oxygen, hemoglobin, and cardiac output.

\[
DO_2 \ (mLs \ O_2/min) = \text{cardiac output} \ (L/min) \times \text{hemoglobin} \ (g/L) \times 1.34 \times \text{oxygen saturation} \ (SpO_2) \times 10
\]

Tissue extraction reflects uptake of oxygen (VO2) by the tissues and is defined as:

\[
VO_2 = \text{cardiac output} \times 13.4 \times \text{hemoglobin} \times (\text{SaO}_2 - \text{SvO}_2)
\]

ScvO2 reflects the balance between oxygen delivery and extraction. The “normal” level of ScvO2 is approximately 75%. The mixed-venous oxygen saturation is measured in the pulmonary arterial system and is, on average, approximately 5% to 7% less than the SvO2 likely due to deoxygenated blood from the coronary sinus.

A defect in any of the 3 components of oxygen delivery may result in shock when tissue demand exceeds tissue supply. For example, a massive pulmonary

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**Table 2. Source Control Techniques**

<table>
<thead>
<tr>
<th>Drainage</th>
<th>Intra-abdominal abscess</th>
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<tr>
<td></td>
<td>Thoracic empyema</td>
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<td></td>
<td>Septic arthritis</td>
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<td>Pyelonephritis, cholangitis</td>
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<td>Débridement</td>
<td>Necrotizing fasciitis</td>
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<td></td>
<td>Infected pancreatic necrosis</td>
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<td>Intestinal infarction</td>
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<td>Mediastinitis</td>
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<tr>
<td>Device removal</td>
<td>Infected vascular catheter</td>
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<tr>
<td></td>
<td>Urinary catheter</td>
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<tr>
<td></td>
<td>Colonized endotracheal tube</td>
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<tr>
<td></td>
<td>Infected intrauterine contraceptive device</td>
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<tr>
<td>Definitive control</td>
<td>Sigmoid resection for diverticulitis</td>
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<tr>
<td></td>
<td>Cholecystectomy for gangrenous cholecystitis</td>
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<tr>
<td></td>
<td>Amputation for clostridial myonecrosis</td>
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</tbody>
</table>

embolism that causes inadequate oxygen saturation results in inadequate tissue perfusion. Likewise, a gastrointestinal hemorrhage can create a shocked state by depleting hemoglobin, and an acute myocardial infarction with cardiogenic shock is a classic example of a shocked state from inadequate cardiac output. In sepsis, each of these 3 components may be threatened.

**Oxygen**

Hyoxia is almost universally present in sepsis indirectly as a result of lung inflammation (ie, acute lung injury [ALI]/ARDS) or directly as a result of pulmonary disease (eg, pneumonia). Therefore, basic principles of airway and ventilator management are essential to reversing respiratory hypoxia.

**Hemoglobin**

Anemia is not necessarily present in the shocked patient but may occur directly from bleeding (eg, gastrointestinal bleed) or indirectly (eg, hemodilution from resuscitation or baseline anemia). Frequently, patients who succumb to sepsis have factors that predispose them to low hemoglobin levels, such as end-stage renal disease or malignancy. Thus, transfusion may be an important aspect of management of the shocked patient. However, there is controversy regarding when and to what value to transfuse patients. Hebert et al reported a trend toward increased 28-day mortality for euvolemic intensive care unit (ICU) patients who received red cell transfusions, leading many clinicians to lower their transfusion thresholds for nonshocked patients to levels of 7 to 8 g/dL. However, the cohort of patients examined by Hebert and colleagues did not include the hypovolemic and shock patient. In contrast, Rivers and colleagues’ EGDT protocol utilized red cell transfusion in the early resuscitation protocol. While the protocol overall reported to an improvement in mortality, identifying the key components of the protocol is difficult. Therefore, in the euvolemic resuscitated patient who is not in shock, a target hemoglobin of 7 to 8 g/dL is consistent with current data. However, in the shock patient (specifically in the early phase of disease), red cell transfusion to levels of 10 g/dL may be more consistent with current data.

**Cardiac Output**

The third component of oxygen delivery is cardiac output or flow. Cardiac output is further defined by stroke volume multiplied by heart rate. Stroke volume is influenced by preload, afterload, and contractility; the manipulation of these 3 variables theoretically promotes optimal flow to tissues. Patients in septic shock need large volumes of fluid for the initial resuscitation to restore preload deficits. According to the EGDT trial, preload was restored by achieving a central venous pressure greater than 8 to 12 mm Hg. An important caveat to note is that central venous pressure reflects just that—pressure and not volume. Therefore, patients with underlying reasons for elevated central venous pressure (ie, chronic obstructive pulmonary disease, cor pulmonale, myocardial dysfunction) may not fit into this simple paradigm, and the clinician should be alert to this potential exception to this generally acceptable rule. Additionally, patients on ventilator support develop increased levels of intrathoracic pressure and therefore increased central venous pressures. In this population, patients may require goal central venous pressures greater than 8 to 12 mm Hg; the Surviving Sepsis Campaign recommendations suggest 12 to 15 mm Hg.

Another mechanism for determining adequate preload is analysis of the Frank-Starling curve specific to the patient. The Frank-Starling curve reflects the principle that increased preload (volume) leads to increased cardiac output up to a point. Thus, when maximum capacity is reached, the heart will no longer increase cardiac output in response to volume. Furthermore, the continued supply of volume in this state may lead to decreased cardiac output. To determine the physiologic state of an individual patient in reference to this curve, a “fluid challenge” can be performed in which cardiac output is measured prior to and after the infusion of fluid. A significant increase in cardiac output may indicate that a patient still requires additional fluid. An important corollary to understanding this concept is to recognize that a “normal” patient, by definition, will be on the supply-dependent portion of the Frank-Starling curve. That is, if a fluid challenge were performed in a patient not in septic shock, an increased cardiac output would still be expected with an increased volume of fluid. Thus, a fluid challenge should be performed and evaluated only in patients who are exhibiting signs that may indicate tissue hypoperfusion (ie, low blood pressure, elevated lactic acid levels, decreased urine output). Within that patient population, this curve becomes an important adjunct of fluid management.

Patients in septic shock often have myocardial suppression. Parker and colleagues described the “typical” myocardial suppressive pattern as being that of biventricular dilation with decreased contractility and a concurrent increase in cardiac output. While this pattern may describe the majority of patients in septic shock, a subset of patients may fail to compensate adequately and have depressed cardiac output as well. In
patients with depressed cardiac output, inotropic agents may be of benefit. In the EGDT trial, myocardial suppression with depressed cardiac output was identified by low ScvO2 in the presence of normal or high central venous pressure. For these patients, inotropic support was initiated.

Low afterload is the common finding in septic shock, although early and late shock could also be associated with excessively high afterload. In early septic shock, patients may present with high mean arterial pressures potentially requiring afterload reduction. More typically, vasodilator shock predominates and vasopressor support may need to be initiated. One important caveat is that preload should be adequately restored prior to initiation of vasopressors. At times, vasopressor therapy may need to be initiated prior to adequate restoration of preload if the level of hypotension is life-threatening or causing severe hypoperfusion. Norepinephrine followed by dopamine are first-choice vasopressors. In cases of severe tachycardia, phenylephrine can be considered. Epinephrine should only be considered only in refractory cases. As discussed previously, vasopressin levels may be relatively depleted in sepsis, and therefore replacement doses of vasopressin may help in refractory shock. Vasopressin usage remains controversial at this time because of lack of evidence of proven survival benefit; an ongoing multicenter trial hopefully will help define the role of this therapy. Corticosteroids should also be considered in cases of refractory shock.

CORTICOSTEROIDS

The use of corticosteroids in septic shock is a somewhat controversial topic. Because corticosteroids mitigate inflammation, are integral to vascular integrity and permeability, and contribute to vascular contractive properties, in theory, they should be ideal for the treatment of septic shock. However, early studies utilizing steroids for sepsis failed to show improvement in mortality, with some indicating increased mortality mostly due to nosocomial infections. In contrast, several recent studies of septic shock have shown that steroids may be beneficial. These 2 groups of studies essentially differed in regard to steroid doses and patient selection. The unsuccessful early trials used very high doses of corticosteroids, whereas the recent successful trials used lower dose (more physiologic) replacement of steroids and careful patient selection. The contrast between groupings of trials in relationship to dosage was shown in a recently published meta-analysis by Minneci et al, which demonstrated that trials utilizing corticosteroids at physiologic dosages had improved outcomes in comparison with trials that utilized supra-physiologic dosages.

The concept of “relative” adrenal insufficiency was recently introduced to help further discern a patient population who would benefit from corticosteroids, although the differentiation of patients remains controversial. Annane and colleagues performed a randomized, prospective trial in which 300 patients with refractory septic shock were randomly assigned to physiologic-dose corticosteroid therapy or placebo. Overall, there was no mortality difference between the groups, although a trend toward decreased mortality was found in the steroid group. The cohort of patients with relative adrenal insufficiency (defined a priori by failure to raise cortisol levels > 9 µg/dL after 250 µg of cosyntropin) had a 10% improvement in mortality compared with the placebo arm.

The Surviving Sepsis Campaign recommends using physiologic dosages of corticosteroids in patients with refractory septic shock and leaves open the “option” for defining those who have relative adrenal insufficiency and therefore discontinuing therapy for those who do not. However, as with antibiotics, corticosteroid therapy should not be withheld while awaiting results of the cosyntropin stimulation test.

TIGHT GLYCEMIC CONTROL

Tight glycemic control recently has been emphasized in the care of critically ill patients. A 2001 Belgian study of surgical ICU patients who remained in the ICU for more than 5 days showed a 10% mortality benefit in those with tighter glycemic control (glucose level between 80 and 110 mg/dL) through use of intensive insulin therapy. The subgroup of septic patients in this cohort was found to have improved mortality, and these results have been extrapolated to potentially apply to all septic patients.

Debate has centered on whether improved outcome is derived from the properties of insulin infusion or the beneficial effects of glucose control. Some evidence suggests that the improved mortality with tighter glycemic control is not simply an effect of receiving increased amounts of insulin. In a study of 523 ICU patients in London, those who received greater amounts of insulin had higher mortality. Improved mortality correlated with glucose control below 145 mg/dL, as opposed to cumulative insulin dose. The benefit of glycemic control appears to result more from aggressive avoidance of the detrimental effects of hyperglycemia rather than the potential therapeutic effect of insulin. Based on the studies discussed above, the Surviving Sepsis Campaign recommends maintaining a glucose level below 150 mg/dL.
VENTILATOR MANAGEMENT

ALI and ARDS are common sequelae of severe sepsis. ALI is defined as diffuse, bilateral pulmonary infil-
trates, a PaO2/FIO2 (fraction of inspired oxygen) ratio of
300 torr or less, and a pulmonary artery occlusive pres-
sure less than 18 mm Hg (or absent signs of left atrial
hypertension). ARDS comprises ALI but with more
severely compromised oxygenation (ie, PaO2/FIO2 ratio
is ≤ 200 torr).

In severe sepsis, cytokine activity or direct cytotoxic
activity by molecular components of offending path-
ogens can cause damage to the alveolar-capillary wall
endothelium and epithelium. This damage results in
alveolar edema and hyaline membrane formation, sur-
factant suppression, and eventual fibrosis if not re-
versed. These cellular changes result in decreased pul-
monary compliance and increased dead space with
associated hypoxia.

Recent evidence suggests that certain ventilation set-
tings can actually increase the problem. Overdistension
of alveoli, including atelectatic alveoli in ALI or ARDS,
can trigger proinflammatory cytokines that contribute
to further pulmonary and systemic injury. To avoid
overdistension, judicious use of tidal volume may be
necessary. The ARDS Network conducted a study com-
paring “traditional” versus low tidal volume ventilator
strategies in the management of patients with ALI and
ARDS.44 The study reported that patients with tidal vol-
umes in comparison with current practice of the time
and argue that the study essentially harmed the control
group rather than provided benefit to the therapy arm.
Nonetheless, consensus opinion at this time agrees with
maintenance of a plateau pressure of 30 cm H2O or less.
Whether all patients should be maintained at 6 mol/kg
of predicted body weight or only those with excessive
plateau pressures remains controversial (Table 3).

DROTRECOGIN ALFA

Many clinical sepsis trials investigating the efficacy of
medications targeted at inflammatory and coagulant host
responses to infection have failed to show survival advan-
tages.45,46 However, a recent multicenter clinical trial
reported improved survival in patients with severe sepsis
reported recombinant activated protein C (drotrecogin
alfa) compared with placebo.47 Drotrecogin alfa is the
only widely accepted drug specific to the therapy of sepsis.
Activated protein C is an endogenous anticoagulant with
anti-inflammatory properties, and reduced levels have
been associated with poor outcomes.48 Based on the
unique physiology of meningococcal disease and purpu-
ra fulminans, activated protein C may have a particularly
important role in these diseases.

In the PROWESS trial involving 1690 randomized
patients, the 28-day mortality rate in those receiving
drotrecogin alfa was significantly lower (24.7%) com-
pared with the placebo group (30.8%) (P = 0.005).47
The number of patients needed to treat to save one life
was 16. This survival advantage appears to be in patients
with sepsis and high severity of illness scores (APACHE-
II score ≥ 25) but not in patients with less severe sepsis.
Because activated protein C is an anticoagulant, pa-
tients with increased risks of bleeding were excluded

Table 3. ARDSNET Ventilator Management

| Assist control mode—volume ventilation |
| Reduce Tv to 6 mL/kg predicted body weight<sup>a</sup> |
| Keep plateau pressure < 30 cm H2O—reduce Tv as low as 4 mL/kg predicted body weight to limit plateau pressure |
| Maintain SaO2/SpO2 88%–95% |

Anticipated PEEP settings at various FIO2 requirements:

<table>
<thead>
<tr>
<th>FIO2</th>
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FIO2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; SaO2 = arterial oxygen saturation; Tv = tidal volume.

<sup>a</sup>Predicted body weight calculation: Male: 50 + 2.3 (height [in] – 60) or 50 + 0.091 (height [cm] – 152.4); Female: 45.5 + 2.3 (height [in] – 60) or 45.5 + 0.91 (height [cm] – 152.4).
from this trial, and generalizing the safety and efficacy results to other patient populations may not be valid (Table 4). While treating appropriate patients with activated protein C is expensive, cost-effectiveness analyses have demonstrated it to be comparable with many other expensive treatments widely accepted by the medical profession and society.

**CASE PRESENTATION**

A 57-year-old woman with a history of diabetes mellitus and hypertension presents with the chief complaint of weakness and shortness of breath. She relates that over the past several days she has felt increasingly weak to the point where she can no longer ambulate. She has had some pain with urination and right flank pain.

On examination, the patient is found to have a temperature of 38.5°C, heart rate of 130 bpm, blood pressure of 130/70 mm Hg, respiratory rate of 28 breaths/min, and an oxygen saturation of 92% on room air. In general, the patient is awake and alert but appears to be anxious. She has dry mucous membranes and no jugular venous distension. Her heart, lung, and gastrointestinal examinations are normal with the exception of some right costovertebral angle tenderness. She has some trace peripheral edema in the lower extremities, but the remainder of the examination is normal.

Laboratory analysis reveals a normal chest radiograph and electrocardiogram. Her leukocyte count is 9000/mm³ with 30% bands and 60% neutrophils. Electrolyte panel reveals a bicarbonate concentration of 15 mEq/L, blood urea nitrogen of 40 mg/dL, and creatinine level of 1.4 mg/dL. Troponin is found to be 2.0 ng/mL and a lactic acid level is 4.3 mmol/dL. Urinalysis shows 578 leukocytes and 50 erythrocytes with positive leukocyte esterase. The patient’s calculated APACHE score is 19.

1. At this point in your assessment, how would you classify the patient’s disease process?
   - A) SIRS
   - B) Sepsis
   - C) Septic shock
   - D) Severe sepsis
   
   The correct answer is D. The patient is a 57-year-old woman with a history, physical examination, and laboratory analysis consistent with urosepsis. She has 4 SIRS criteria (respirations > 20 breaths/min, temperature > 38°C, heart rate > 90 bpm, bands > 10%). In addition, the patient has an identifiable source of infection (positive urinalysis). The patient has involvement of at least 3 organ systems including the kidneys (elevated blood urea nitrogen/creatinine), heart (troponin of 2.0 ng/mL), and lungs (PO₂ of 57 mm Hg). The patient does not exhibit hypotension, but given her history of hypertension, it is unclear whether her current blood pressure is 40 mm Hg lower than her usual reading. Thus, without hypotension or relative hypotension, the patient would be classified as severe sepsis (sepsis plus more than 1 organ system failure). Despite the current “book” definition of shock, the essence of shock is tissue hypoperfusion. The patient’s elevated lactic acid level and degree of acidosis are evidence of tissue hypoperfusion. Patients in this state need to be recognized and treated expeditiously even if they do not meet the currently derived strict criteria for shock (ie, refractory hypotension).

2. Which of the following intervention(s) should be employed for the patient at this time?
   - A) Corticosteroids
   - B) EGDT
   - C) Activated protein C
   - D) Antibiotics
   - E) Low tidal volume ventilation
   - F) Tight blood glucose control

   The correct answers are B and D. The patient meets criteria for EGDT (more than 2 SIRS criteria plus lactic acidosis [≥ 4 mmol/L] or hypotension). In addition, empiric antibiotics should be rapidly administered. Glucose levels are relatively low and no therapy is needed at this time. Since the patient has an APACHE II score of 19, activated protein C would not be indicated.
REFERENCES


