

# SEPTIC SHOCK: REVIEW AND ANESTHETIC CONSIDERATIONS

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## Introduction

During management of septic patients, an anesthesiologist must pay particular attention to intravascular volume status and cardiovascular function. Ischemia and sepsis can have profound effects on the body, and the anesthesiologist should be able to anticipate dysfunction and be able to plan treatment accordingly, including compliance of standard care for sepsis, avoidance of specific anesthetics that may exacerbate shock, and proper monitoring of the patients intraoperatively and postoperatively. Furthermore, one must also examine the patient, evaluate, and treat any potential complications associated with septic shock.

## Definition

Because varying definitions of sepsis and septic shock were used in the past, standardized definitions were produced by The American College of Chest Physicians and the Society for Critical Care Medicine Consensus Conference on Standardized Definitions of Sepsis in 1991<sup>1</sup>. Sepsis is defined as an infection-induced syndrome involving 2 or more manifestations of systemic inflammatory response syndrome: (1) temperature > 38 degrees or < 36 degrees; (2) heart rate > 90 beats/min; (3) respiratory rate > 20 breaths/min or PaCO<sub>2</sub> < 32 mmHg; and (4) white blood cell count > 12000/microliter, < 4000/microliter or > 10% immature (band) forms<sup>2</sup>. Septic shock is an increasingly severe sequela of sepsis

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involving hypotension despite adequate fluid resuscitation as well as the presence of perfusion abnormalities or organ dysfunction. The latter are evident in resultant lactic acidosis, oliguria, obtundation, and so forth.

### **Epidemiology**

A study by 8 academic medical centers of 1342 episodes of sepsis seen during 16 consecutive months reported a rate of 2 cases per 100 hospital admissions in the U.S. of these cases, 55% occurred in the ICU, 12% in emergency departments and 33% in non-ICU patient care units<sup>3</sup>. More recent data suggest that the yearly incidence of sepsis is approximately 50-95 cases per 100,000. Moreover, the incidence has been growing by 9% each year<sup>4</sup>.

Gram-negative bacteria typically account for the etiology of 35 to 40% in occurrence of cases of sepsis but has decreased to 25-30% in 2000<sup>5</sup>. Gram-positive bacteria cause 30-50% of cases, and polymicrobial infections account for 25%<sup>5</sup>.

Approximately 50% of septic patients develop septic shock, which has an attributed mortality rate of 45%<sup>6</sup>. The most frequent sites of infection are the lungs, abdomen, and urinary tract.

Complications from septic shock include ARDS, disseminated intravascular coagulopathy (DIC) and renal failure, accounting for 18%, 38% and 50% of cases, respectively<sup>7</sup>. Men as well as older adults are slightly more predisposed to developing septic shock than women<sup>8</sup>.

### **Pathophysiology**

Sepsis develops from a nidus of infection (UTI, pneumonia, cellulites, etc) to an invasion of the bloodstream or proliferation at the site of infection. Toxins from the infecting organism, especially endotoxin from gram-negative bacteria, elicit a systemic response consisting of the release of endogenous mediators and activation of complement, kinins and coagulation factors<sup>9,10</sup>. Cytokines such as TNF-alpha and IL-1 are among the most important of the endogenous mediators, initiating a cascade

resulting in the formation of secondary mediators such as IL-6, IL-8, platelet activating factor, prostaglandins and leukotrienes; activation of neutrophils, the complement system and vascular endothelial cells; synthesis of acute phase reactants; and, activation of clotting and the kinin cascades. Interleukin-8 has a chemotatic effect on neutrophils, and appears to play an important role in maintaining tissue inflammation. Arachidonic acid metabolites thromboxane A2, prostacyclin and prostaglandin E2 promote fever, tachycardia, tachypnea, ventilation-perfusion abnormalities and lactic acidosis. Activation of the complement system promotes vasodilation, increased capillary permeability, activation and enhancement of phagocytosis, and protease-mediated lysis of pathogens. The activated kinin system causes further vasodilation and increase of capillary permeability and of phagocytic activity. The overall outcome of this series of events constitutes the entity referred to as SIRS<sup>11</sup>.

### Clinical Manifestations

Common manifestations of sepsis are fever, rigors, myalgias, tachycardia, tachypnea, hypoxemia, proteinuria, leukocytosis, eosinopenia, hypoferrremia, irritability, lethargy, and hyperglycemia (especially in diabetics). Less commonly observed clinical features include hypothermia, lactic acidosis, ARDS, azotemia, oliguria, leucopenia, thrombocytopenia, DIC, anemia, stupor, upper GI bleeding, cutaneous lesions, fundoscopic lesions and hypoglycemia<sup>12,13</sup> [Table 1].

*Table 1*  
*Clinical Manifestations*

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Common	fever, rigors, myalgias, tachycardia, tachypnea, hypoxemia, proteinuria, leukocytosis, eosinopenia, hypoferrremia, irritability, lethargy, and hyperglycemia (especially in diabetics)
Less common	hypothermia, lactic acidosis, ARDS, azotemia, oliguria, leucopenia, thrombocytopenia, DIC, anemia, stupor, upper GI bleeding, cutaneous lesions, fundoscopic lesions and hypoglycemia.

The demanding burden of organ failure is responsible for mortality during sepsis, and therefore effective treatment is critical. Indeed, for every organ system that fails, the risk of death increased by 15-20%<sup>14</sup>. Pulmonary dysfunction occurs frequently in these patients, presents early, and tends to persist. On the other hand, shock, which occurs early as well, results in fatality or rapid resolution. Hours or even days after the onset of sepsis, abnormalities of the liver, coagulation, and central nervous system arise. Moreover, prognosis parallels the severity of failure<sup>15</sup>.

Mental status, urinary output, and skin perfusion help establish a patient's circulatory status. When the systolic blood pressure is less than 90 mmHg, the patient is considered to be in shock. Initially, low cardiac output, decreased cardiac filling pressures (pulmonary capillary wedge pressures less than 8 mmHg), and normal to increased systemic vascular resistance characterize the beginning of shock. Later, septic shock, is marked by a decline in peripheral vascular resistance and an increase in cardiac output in response to the fall in PVR. This response is the body's mechanism to maintain adequate perfusion, despite the presence of myocardial depressant activity exerted by TNF-alpha, PAF, IFN-gamma, arachidonic acid metabolites and other endogenous factors. Their effect may decrease ejection fraction to as little as 20%<sup>16</sup>. At this stage of septic shock, hypovolemic patients show an improvement in blood pressure in response to IV fluids. However, over hours or days, as myocardial depressant substances continue to exert their effects, further depression of cardiac function occurs. The combination of vasodilation, severe capillary leak, and reduced cardiac output results in declining blood pressure<sup>17</sup>. Transesophageal echocardiography may show left ventricular dysfunction. Once this falling blood pressure becomes refractory to fluid resuscitation as well as inotropic agents and vasopressors such as dopamine and phenylephrine, death can occur due to hypotension or organ failure brought on by the hypoperfusion<sup>15,17</sup>.

Additionally, the hypoperfusion may also manifest as lactic acidosis. This acidosis reflects the global tissue ischemia secondary to inadequate oxygen delivery<sup>19</sup>. The disordered local autoregulation and/or cellular dysfunction prevents any regional ischemia from responding to oxygen

delivery. Sodium bicarbonate is commonly used to treat acidosis when the pH drops below 7.2, although it is difficult to show that this improves cardiovascular performance<sup>15</sup>.

Increased minute ventilation is required since sepsis places extreme demands on the lungs. Lung compliance is decreased, airway resistance is increased, and skeletal muscle efficiency is impaired<sup>19</sup>. Tachypnea and arterial hypoxemia may be seen during sepsis, and these symptoms may progress to adult respiratory distress syndrome (ARDS). ARDS is a major complication of sepsis and can occur early or late. Injury to the microcirculation during sepsis causes an increase in alveolar and capillary permeability, leading to lung edema. This manifests clinically as dyspnea, hypoxemia, and an abnormal chest x-ray<sup>20,21</sup> [Table 2].

Table 2  
Manifestations of ARDS

ARDS symptoms	Dyspnea
	Hypoxemia
	Abnormal chest x-ray

The risk of aspiration and respiratory muscle oxygen requirements are both reduced with well-timed tracheal intubation and mechanical ventilation, with up to 85% of patients requiring 7 to 14 days of mechanical ventilatory support<sup>19</sup>. In addition, supplemental oxygen and the use of positive end-expiratory pressure are acceptable modalities to maintain arterial oxygen saturations around 90%<sup>15</sup>.

Azotemia, oliguria and active urinary sediment are manifestations of the acute renal failure caused by sepsis and septic shock. Hypotension, dehydration and renal ischemia due to hypoperfusion are instrumental in producing these signs and symptoms of renal dysfunction<sup>22</sup>. Although oliguria secondary to hypotension is common, anuria is rarely found. In fact, patients requiring dialysis for renal failure occurs in less than 5% of the septic patients<sup>19</sup>.

Commonly, coagulation defects are seen in septic patients, possibly reflecting a vitamin K deficiency and/or effects on factors II, VII, IX, and X<sup>18</sup>. Furthermore, prothrombin and, in severe cases, plasma

thromboplastin times may be prolonged. One may find thrombocytopenia secondary to platelet destruction, as well as direct activation of the coagulation cascade and fibrinolysis<sup>15</sup>. Ultimately, disseminated intravascular coagulopathy may ensue. Laboratory studies will reveal thrombocytopenia, prolonged thrombin time, fibrin degradation products, and decreased levels of fibrinogen and factors V and VIII<sup>24,25</sup>. Other frequent findings in sepsis are isolated neutropenia, neutrophilia, and thrombocytopenia.

Central nervous system dysfunction, or septic encephalitis, may present early in the course of sepsis. This early presentation holds true especially for the elderly population<sup>15</sup>. Mental changes may result from the combined effects of hypoxemia, hypotension, sedatives, and analgesics. Arterial hypoxemia or intracranial hemorrhage is usually the underlying cause of a decreased Glasgow Coma Scale if medications are ruled out<sup>19</sup>.

Endotoxin, release of cytokines, and hemolysis account for elevated levels of bilirubin, transaminases, and alkaline phosphatase, evident in sepsis and septic shock. Less commonly, hypotension and hypoperfusion accompanying septic shock can result in acute ischemic hepatitis or ischemic bowel necrosis. Other gastrointestinal complications include “stress” ulcers and ileus<sup>26</sup>. Endocrine abnormalities in the form of hyperglycemia may be one of the first clues to infection in a septic diabetic patient, but this finding has also been seen increasingly in non-diabetic patients with sepsis. Rarely, hypoglycemia may also manifest in sepsis and septic shock.

## **Diagnosis**

Septic shock is a clinical diagnosis. A thorough history and physical examination are critical to diagnosis. Generally, sepsis should be suspected in a patient presenting with hypotension, reduced perfusion and an obvious source of infection (i.e., pyelonephritis). Clinical features such as widened pulse pressure, flushing of the skin and hyperventilation may also be present. Laboratory tests often used include CBC, DIC panel,

electrolytes, liver function tests, renal function tests, ABGs, UA, and blood and urine cultures. Cultures of CSF and sputum and plain films should be obtained if symptoms are suggestive<sup>26</sup>. One laboratory marker found to be useful is discriminating septic shock from nonseptic shock was procalcitonin<sup>28,29</sup>. While C-reactive protein levels also rise in sepsis, this marker does not have as good a linear correlation with occurrence of the disorder as procalcitonin<sup>30</sup>. The differential diagnosis of septic shock includes hypovolemic, cardiogenic and anaphylactic shock.

### **Treatment**

Treatment is targeted toward restoration of organ perfusion and control of the infection precipitating sepsis<sup>31</sup> [Table 3 & 4]. Central venous pressure should be restored to 8-12 mmHg; mean arterial pressure should reach 65-90 mmHg; and central venous oxygen saturation should be greater than 70% with treatment<sup>4</sup>. Correction of inadequate perfusion begins with administration of normal saline or lactated Ringer solution. Some markers to monitor improvement are patient mental status, skin perfusion and urine output. Lack of response to IV fluids, as may occur in septic shock, necessitates use of vasopressors. Dopamine, having both vasopressor and inotropic effects, is considered a first-line drug<sup>32</sup>. Dobutamine, an inotrope, is often initiated with dopamine<sup>33</sup>. If these agents prove inadequate, norepinephrine, a potent vasoconstrictor, is given<sup>34,35</sup>. If all 3 agents fail, epinephrine is initiated as the drug of last resort<sup>36</sup>. Once pharmacologic agents become necessary to combat hypoperfusion, the risk of death climbs to 80%<sup>37</sup>.

Sources of infection such as indwelling IV catheters should be removed. If the source of infection involves retained necrotic tissue or an abscess, surgical intervention should be carried out without delay. Controlling sepsis requires immediate institution of antibiotics as early as possible.

Table 3  
Treatment Guidelines<sup>15</sup>

Abnormality	Therapy	Goal
<b>Infection</b>	Surgical Drainage; Antibiotics	Eliminate infection
<b>Cardiovascular Dysfunction</b> <i>Hypotention</i>	Intravascular volume resuscitation; vasopressors	Maintain mean arterial pressure above 60 mmHg; pulmonary capillary wedge pressure between 14-18 mmHg
<i>Hypoperfusion of tissue</i>	Intravascular volume resuscitation; vasopressors; inotropic agents	Hb > 10 g/dL; O <sub>2</sub> sat > 88%; Cardiac index > 4 L/min/m <sup>2</sup>
<b>Pulmonary Dysfunction</b>	Supplement with oxygen; a-mechanical ventilation	O <sub>2</sub> sat > 88%; Minimize A-a gradient
<b>Renal Dysfunction</b>	Intravascular volume resuscitation; vasopressors, inotropes	Normalization of creatinine concentration; adequate urine output
<b>Liver Dysfunction</b>	Intravascular volume resuscitation; vasopressors	Normalization of serum aminotransferase concentrations

Table 4  
Treatment

Action	Complication	Treatment
Correction of inadequate perfusion		Normal saline or lactated Ringer solution
	Lack of response to IV fluids	Dopamine (first line), Dobutamine, Dopamine
	If above agents fail	Norepinephrine
	Last resort	Epinephrine
Remove sources of infection		Ex. Remove indwelling catheter
Control sepsis		Antibiotics as early as possible

Table 5  
Treatment by Antibiotics

Timing	Patient population involved	Antibiotic
Before microbe identified	All patients	Broad-spectrum
	All patients-empiric coverage	Ceftriazone + gentamycin
		Imipenem + gentamycin
After microbe identified	Depends on patient	
	Immunosuppressed	Ceftazidime, imipenem, or meropenem alone
	Pt has atypical community acquired pneumonia	Add erythromycin
	Patient with anaerobe infection (intraabdominal abscess)	Add metronidazole or clindamycin
	Patient infected with gram (+) organism (IV drug users)	Add oxacillin or vancomycin
	Patient has urosepsis	Add Vancomycin

Initially, while culture and sensitivity results are pending, broad-spectrum coverage effective against both gram-positive and gram-negative bacteria is the standard of care (Table 5). Combination therapy involving a third-generation cephalosporin (ceftriazone, cefotaxime, ceftazidime) or an anti-pseudomonal beta-lactamase susceptible penicillin (imipenem) plus an aminoglycoside (gentamicin, tobramycin) is considered effective empiric coverage<sup>38</sup>. Once microbial etiology is demonstrated by culture, empiric coverage can be modified according to clinical and epidemiologic characteristics of the patient. Thus, the immunosuppressed patient may be covered with ceftazidime, imipenem or meropenem alone. Patients with atypical or community acquired pneumonia would benefit from addition of erythromycin. An infection likely to involve anaerobes, such as intraabdominal abscess, requires the addition of metronidazole or clindamycin. If gram-positive infection is suspected, as in IV drug users, oxacillin or vancomycin should be added to the regimen. Vancomycin is also added when urosepsis is the cause of infection<sup>39</sup>. Rapid treatment with antibiotics is key to survival. However, there is evidence to suggest that once sepsis advances to shock antibiotic

treatment may no longer be effective<sup>40</sup>.

Septic shock continues to have rates of mortality despite aggressive management with fluid resuscitation, broad-spectrum antibiotics, and surgical intervention. More recent interventions have been devised on the premise that neutralizing bacterial toxins and the inflammatory mediators they incite, could stop or slow down the syndrome of septic shock<sup>41</sup>. However, antibodies to endotoxin have not shown an overall survival benefit for patients with sepsis<sup>42,43</sup>. TNF-alpha plays perhaps the key role in the inflammatory response seen in sepsis. Both TNF-alpha and IL-1, another important mediator, have been widely studied in septic patients. So far, antibodies to TNF-alpha have not demonstrated an improvement in survival<sup>44</sup>. Similarly, studies using an IL-1 receptor antagonist (naturally occurring protein that competes with the binding of IL-1 to its cell surface receptors) found no consistent reduction in mortality among patients with sepsis<sup>45</sup>.

One anti-inflammatory agent shown to be effective in the treatment of sepsis is human recombinant activated protein C (drotrecogin alpha). Activated protein C works via anti-inflammatory and anticoagulation effects. It inhibits factors Va and VIIa and thrombin production, and activates fibrinolysis. Its anti-inflammatory effects include inhibiting monocyte production of such cytokines as TNF-alpha, IL-6 and IL-1, as well as preventing cell adhesion to endothelium. This agent has been shown to significantly reduce the 28-day mortality rate in septic patients<sup>46</sup>. While the efficacy of activated protein C is applicable to septic patients regardless of such characteristics as age and severity of illness, it has only been used to treat patients who had multiorgan dysfunction and a high likelihood of mortality. A major risk of this treatment is serious bleeding<sup>46</sup>.

Another form of treatment showing promise as an adjunct to standard treatment is early goal-directed resuscitation [Table 6]. A study applied this intervention within the first 6 hours of patient arrival in the ED and used the following parameters to guide treatment: (a) maintenance of central venous pressure from 8 to 12 mmHg; (b) protocol administering sequentially fluids, pressors, blood transfusions and

mechanical ventilation; and (c) hematocrit of 30%. The outcome was a 15% reduction in hospital mortality of 130 patients with sepsis and septic shock<sup>47</sup>.

*Table 6*

<b>Early goal-directed resuscitation</b>
Maintenance of central venous pressure from 8 to 12 mmHg
Protocol administration sequentially fluids, pressors, blood transfusions and mechanical ventilation
Hematocrit of 30%
Insulin administration

Finally, tight control of blood glucose with insulin administration has demonstrated a significant reduction in mortality among septic patients in multiorgan failure. These findings are applicable to both diabetic and nondiabetic patients<sup>48</sup>.

### **Perioperative Anesthetic Management**

Anesthetic management in septic patients is heavily influenced by intravascular volume status and cardiovascular function<sup>18</sup>. Sufficient preoperative systemic blood pressure is not indicative of adequate volume status, and therefore, heart rate, urine output, and mental status should all be considered when evaluating the volume. Intravenous fluids as well as vasopressors and inotropic agents can help hemodynamically stabilize the patient before induction<sup>15</sup>.

Preoperatively, the anesthesiologist should anticipate dysfunction of the gastrointestinal tract secondary to ischemia. The septic patient should be managed as if a full stomach is present, and therefore a nasogastric tube may be considered<sup>49</sup>. Currently, studies of dopamine, dobutamine, and dopexamine on gastrointestinal blood flow suggest that these inotropic agents did not reach the microcirculation in the gastrointestinal

tract despite increasing cardiac output<sup>50</sup>. In addition, these patients are frequently at higher risk for aspiration since ileus is often associated with sepsis. Arterial blood gases obtained preoperatively may be used to predict the need for mechanical ventilation after the completion of surgery. Furthermore, hypoglycemia may ensue patients on total parenteral nutrition have their feeding suddenly removed<sup>15</sup>.

Preparation for surgery includes having adequate blood products available and continuing antibiotic treatment. Any vasopressors should be prepared and on hand before induction of anesthesia<sup>49</sup>. Presently, after studying eight different randomized control trials, Mullner et al. concluded that no vasopressors have been found to be superior to other agents in treatment of shock<sup>51</sup>.

Although there are no specific anesthetic techniques for induction or maintenance, ketamine may prove useful for induction as it is unlikely to decrease systemic vascular resistance rapidly. Indeed, studies have shown that ketamine preserves sympathetic drive although it displays intrinsic myocardial depressant properties<sup>52</sup>. Theoretically, succinylcholine may promote the release excessive potassium in the presence of prolonged intra-abdominal sepsis<sup>18</sup>. Furthermore, if renal failure presents during sepsis, the anesthesiologist should be prepared for management or even dialysis during the operation. In fact, if dialysis is anticipated preoperatively, it may prove useful to insert an appropriate dialysis catheter after cannulation of a central vein has been performed<sup>49</sup>. In addition, animal studies have shown a decreased need for anesthetics during sepsis<sup>53</sup>.

Severe cases of sepsis may lead to multiple organ failure (MOF). One method of treatment for these conditions is plasma exchange, or using plasma as replacement therapy. This, along with standard intensive care, has, in fact, proved to be effective in reversing the progression and increasing patient survival<sup>54</sup>. Plasma exchange as rescue therapy in multiple organ failure including acute renal failure. Once MOF develops, preventive measures come to the forefront. Changes in the cellular O<sub>2</sub> supply can initiate or complicate MOF. This scenario may result in hypoxic organ damage, secondary ischemia-reperfusion injury mediated

by neutrophils, and increased injury secondary to activation of cytokines<sup>55</sup>. The situation calls for O<sub>2</sub> delivery and maintenance with concomitant correction of acid-base balance and gas exchange. Goal-oriented hemodynamic therapy to achieve supranormal values in O<sub>2</sub> delivery and VO<sub>2</sub> (O<sub>2</sub> consumption) has aided organ dysfunction<sup>55</sup>. In fact, studies have revealed that surgical patients with poor cardiovascular reserve have a worse postoperative prognosis stemming from the lack of perfusion; however, perioperative cardiac output augmentation has led to a decrease in mortality and morbidity<sup>56</sup>.

Intraoperative monitoring may be facilitated by the use of arterial and large bore intravenous catheters. Moreover, central venous or pulmonary artery catheters may prove to be helpful. Others have used transesophageal echocardiography as another method for evaluating volume status and inotropic efficiency<sup>15</sup>. Given that carbon dioxide production may be amplified in septic patients, capnography should be used to adjust minute ventilation. Since the pyrexia of sepsis may be offset by substantial heat loss and evaporation from debrided areas, monitoring of core temperature is necessary. For these reasons, intravenous fluid warmers and peripheral warming blankets may possibly aid in maintenance of temperature homeostasis<sup>49</sup>.

Postoperative intensive care unit management includes constant monitoring of vital signs. Mechanical ventilation is often continued after surgery especially when dealing with persistent hemodynamic instability or if it is necessary to maintain adequate circulation with inotropic support<sup>15</sup>.

## Summary

Sepsis and shock are severe conditions that, when together, may cause multiple organ failure. The anesthesiologist must be able to take a careful history and physical, as well as be aware that additional tests are necessary to assess the patient status, as preoperative systemic blood pressure is not indicative of adequate volume status. In preparation for surgery, one must anticipate dysfunction and have adequate blood

products and antibiotic at hand. Ketamine is notable for induction in these patients because it is less likely to decrease systemic vascular resistance too quickly. One must not take this lightly, as death may ensue if proper management is not taken.

*The authors have no relationships with pharmaceutical companies or products to disclose, nor do they discuss off-label or investigative products in this lesson.*

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