

Sepsis: Diagnosis and Management

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Faculty Disclosure

Contributing faculty, Patricia Lea, RN, MEd, CCRN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure

The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare professionals who work with patients who present with sepsis, including nurses and physicians.

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The purpose of CME Resource is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Disclosure Statement

It is the policy of CME Resource not to accept commercial support.

Course Objective

The purpose of this course is to provide healthcare professionals with evidence-based recommendations so they may optimally manage the patient who presents with sepsis and septic shock and minimize adverse outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define the various degrees of sepsis, and describe the history and incidence of sepsis relative to mortality.
2. List the risk factors associated with the development of sepsis.
3. Describe the pathogenesis of SIRS, including the five phases of development, and the pathophysiology of sepsis.
4. List potential organ manifestations related to the development of sepsis.
5. Describe the suggested diagnosis and management of the septic patient.
6. List the diagnostic criteria of suspected SIRS in the pediatric patient.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

DEFINITIONS

The scope of sepsis is broad, and historically, there has been much confusion and lack of consensus in defining the terminology associated with the various degrees of clinical infection. This lack of consensus prompted the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) to convene a conference for the purpose of agreeing on definitions for sepsis and its sequelae. The ACCP/SCCM published their definitions in 1992 [1].

A second sepsis definitions conference was convened in 2001. The purpose of this international conference (sponsored by the ACCP, SCCM, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society) was to modify, where appropriate, the original ACCP/SCCM definitions to reflect current understanding about the pathophysiology of sepsis. Apart from recommending that the list of signs and symptoms of sepsis be expanded to reflect clinical bedside experience, the conference participants found no evidence to support changing the original definitions. These definitions have been widely used since their introduction in 1992 [2].

Infection is defined as the invasion of a normally sterile host tissue by microorganisms or the inflammatory response of a host to an infection. Bacteremia is defined as the presence of viable bacteria in the blood.

Sepsis is defined as a systemic inflammatory response arising from infection, leading to widespread tissue injury and manifested by two or more of the following conditions [1; 2]:

- Hyperthermia (temperature greater than 38°C [100.4°F])
- Hypothermia (temperature less than 36°C [96.8°F])
- Tachycardia (heart rate greater than 90 beats per minute in adults)

- Tachypnea (respiratory rate greater than 20 breaths per minute)
- Hyperventilation (partial pressure of carbon dioxide [PaCO₂] less than 32 mm Hg)
- Leukocytosis (leukocyte count greater than 12,000 cells per mm³)
- Leukopenia (leukocyte count less than 4,000 cells per mm³)

The recognition that noninfectious conditions may also produce a systemic response complicated by tissue injury led researchers to recommend use of the term systemic inflammatory response syndrome (SIRS). This term emphasizes that infection is not the exclusive cause of physiologic changes. The inflammatory response of the host is very important in determining the severity of the illness.

SIRS is an uncontrolled inflammation in response to an insult to the body or an ongoing process that can result in end-organ damage and multisystem failure. Based on epidemiological and clinical evidence, SIRS encompasses a continuum of escalating inflammatory responses to infectious and noninfectious stimuli; end-organ dysfunction and mortality increase with each stage of the advancing inflammatory process. While sepsis is associated with the presence of infection, SIRS may be associated with either infectious or noninfectious insults, including trauma, burns, pancreatitis, anaphylaxis, adrenal insufficiency, pulmonary embolism, myocardial infarction, massive hemorrhage, and cardiopulmonary bypass. Sepsis remains an appropriate term when SIRS is caused by an active infection [1; 3; 4].

Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion abnormality (e.g., lactic acidosis, oliguria, acute alteration in mental status), microvascular dysfunction (e.g., altered leukocyte trafficking, generation of apoptotic microparticles, increased cellular hypoxia), and/or hypotension. This may further progress to sepsis-induced marked hypotension, defined as a systolic blood pressure of less than 90 mm Hg, or a reduction of 40 mm Hg or more from the baseline value, in the absence of

other causes of hypotension. In clinical practice, septic shock (a subset of severe sepsis) represents sepsis-induced hypotension (despite adequate fluid resuscitation), hypoperfusion abnormalities, or organ dysfunction [1; 5].

In an acutely ill patient, altered organ function in more than one major organ constitutes multiple organ dysfunction syndrome (MODS). Organ dysfunction is characterized by various laboratory and clinical assessments, such as [6; 7]:

- A ratio of arterial oxygen tension to fraction of inspired oxygen of 280 or less
- The presence of a metabolic acidosis
- Oliguria (urinary output of less than 0.5 mL/kg of body weight for at least one hour in a patient with a urinary catheter in place)
- An acute alteration in mental status

MODS may be described as “primary” (i.e., organ dysfunction as the immediate result of trauma) or “secondary” (i.e., a consequence of the host response). Because it represents the more severe end of the spectrum of SIRS/sepsis, secondary MODS most commonly complicates severe infection. In some cases, the support of MODS may not improve survival, but merely prolong dying. Given the high costs of supportive care of patients with MODS, the ability to predict which critically ill patients with SIRS/sepsis will develop MODS is important [1].

These definitions are intended to emphasize the dynamic nature of the systemic response to infection and organ system dysfunction and provide a consistent nomenclature for use by clinicians and researchers. The interpretation of clinical trials designed to evaluate conventional and innovative therapies for sepsis should improve if the use of disparate definitions for these terms can be avoided.

HISTORY AND INCIDENCE OF SEPSIS

The first description of multiple organ failure appeared in 1973 in a discussion of three patients who died of distal organ failure that followed ruptured aortic aneurysms. Multiple organ failure was subsequently described as multiple, progressive, or sequential systems organ failure. It was noted that shock or infection alone did not cause the distal organ dysfunction. Other severe insults could set in motion an underlying reaction that would lead to widespread endothelial damage, edema resulting from increased vascular permeability, and impaired availability of oxygen [8; 9; 10].

Sepsis, septic shock, and multiple organ failure are major causes of morbidity and mortality in the U.S., resulting in 750,000 hospitalizations and 215,000 deaths annually. It is estimated that 9.3% of all deaths in the U.S. are a result of sepsis, which equals the number of deaths resulting from myocardial infarction and far exceeds the mortality rates from acquired immune deficiency syndrome (AIDS) or breast cancer [11; 12].

A study of hospital emergency department visits between 2001 and 2004 found that of the 750,000 hospitalizations, more than two-thirds may have initially presented to an emergency department. Cases of suspected severe sepsis account for more than 500,000 emergency department visits annually. The average length of stay in the emergency department is 4.7 hours. However, more than 20% of sepsis patients had a length of stay that exceeded 6 hours, resulting in a substantial burden on facilities nationwide in providing severe sepsis care [13].

The incidence of sepsis has been increasing by an average of 8.7% per year over the last two decades [14]. Between 1993 and 2003, 8.4 million cases of sepsis and 2.4 million cases of severe sepsis were reported. The percentage of severe sepsis cases among all sepsis cases increased from 25.6% to 43.8% during the same time period [15].

The incidence rates of sepsis increase with advanced age. Two-thirds of all sepsis cases occur in people 65 years of age and older, with case fatality rates as high as 40% [16]. Age-adjusted rates for severe sepsis hospitalization and mortality have increased annually by 8.2% and 5.6%, respectively, whereas the fatality rate decreased by 1.4% [15]. Sepsis is more common among men than women, but the fatality rate is greater in women and nonwhite populations [15; 17].

Mortality from sepsis of gram-negative etiology is the cause of 20% to 50% of the overall total number of septic deaths. The figures are now similar for sepsis of gram-positive etiology [18]. Mortality has been reported as high as 60% in patients with underlying medical problems. Among patients who develop the complications of shock and organ failure, mortality can reach 90% [17; 19; 20]. Extent of organ failure contributes to the prognosis, with a greater survival rate in patients with fewer than three failing organs. The risk of death increases as each organ fails [17; 21].

Sepsis was the tenth leading cause of death in the U.S. in 2005 and resulted in the expenditure of \$16.7 billion [12; 22; 23; 24; 25]. Sepsis is not a reportable disease, and it is possible that many deaths attributed to other diseases are actually a result of sepsis.

RISK FACTORS AND PREVENTION

Factors considered important in the development of sepsis include: inappropriate broad-spectrum antibiotic therapy; immunosuppressive treatments, such as cancer chemotherapy; invasive procedures; transplantations; fungal organisms; burns or other trauma; anatomic obstruction; intestinal ulceration; age (the very young and the very old); and progressive clinical conditions, such as malignancy, diabetes, or AIDS [14; 17; 25; 26].

Nosocomial infections are a major cause of sepsis among severely ill patients. Increased risk of nosocomial infection is associated with the presence of underlying chronic disease, alteration in host defenses, prolonged hospital stay, and the presence of invasive catheters or monitoring devices [27]. Pulmonary, urinary tract, gastrointestinal, and wound infections predominate [28; 29]. In hospitalized adult patients, the etiology of sepsis has shifted from being predominantly gram-negative nosocomial infections (*Escherichia coli*, *Klebsiella*, *Enterobacter* species, and *Pseudomonas aeruginosa*) to gram-positive infections (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*). The incidence of sepsis caused by gram-positive infections has increased by 26.3% per year over the last three decades [17]. Multidrug-resistant pathogens, such as *S. aureus*, now account for more than half of all sepsis cases. *S. aureus* is singly responsible for 40% of ventilator-associated pneumonia episodes and most cases of nosocomial pneumonia [17; 25]. Group B streptococcus is a leading cause of neonatal sepsis in the United States [30].

Vascular and monitoring catheters and infusion sets may become contaminated and lead to the development of nosocomial infections and sepsis. The risk of catheter-related sepsis is increased when the IV catheter is placed in a central vein, particularly if the catheter remains in place longer than 3 to 5 days or if the catheter is used for blood sampling [31]. For this reason, consideration should be given to changing the catheter and possibly the insertion site after 72 hours. The risk of contamination of arterial catheters is higher than that observed with venous catheters. Contamination can occur if the system is entered frequently for blood sampling, if the infusate remains in place for more than 48 hours, or if inflammation develops near the catheterized artery [32]. Urinary catheters left in the bladder longer than two weeks often cause infection. Therefore, increased surveillance for signs of urinary tract infections when catheters remain in place beyond a few days is necessary [33].

Central venous catheters (CVCs) are increasingly used in the pediatric population, leading to an increase in CVC-related complications. Implanted ports may be the device of choice when long indwelling times are expected, with consideration given to the patient's age and need for sedation and analgesia during the insertion procedure. Radiograph following the insertion procedure is recommended to ensure correct catheter positioning. Full sterile barrier precautions, strict protocols for catheter care, and prompt removal of the catheter when it is no longer needed are recommended to prevent infectious complications [34].

Bacterial contamination of platelet units (estimated at 1 in 1,000–3,000) results in many occurrences of transfusion-associated sepsis in the United States each year. The AABB (formerly the American Association of Blood Banks) adopted a new standard in 2004 requiring member blood banks and transfusion services to implement detection measures and limit bacterial contamination in all platelet components [35].

Patients who live with malignancy are commonly hospitalized due to infection. Immunosuppressive treatments (or the malignancy itself) can lead to severe infection, which is a frequent cause of death among cancer patients. One in six severe sepsis patients have underlying disease [36].

PATHOGENESIS OF SIRS

The natural defense of the body to an infection, or other assault, involves a number of cellular and humoral factors. They include B and T lymphocytes, macrophages, neutrophils, platelets, tumor necrosis factor (TNF), interleukins, the coagulation factors, and probably several other products [26; 37; 38]. There are five rather distinct phases that describe how these biological products work together to overcome the assault and, paradoxically, how they can interact to cause SIRS and MODS [26; 39].

FIRST PHASE: THE LOCAL RESPONSE

An infection, injury, burn, or similar process can initiate a response that causes the release of various proinflammatory mediators in the immediate area of involvement. Among others, these include the cytokines, eicosanoids, and platelet-activating factors. In an attempt to limit or ameliorate the local injury, these mediators act to remove damaged tissue, stimulate new tissue growth, and combat the spread of neoplastic cells, pathogenic organisms, and antigens. To counteract the effects of these mediators and prevent them from causing damage, the body soon produces a set of anti-inflammatory substances, such as interleukins and TNF receptors [26; 39].

SECOND PHASE: THE EARLY SYSTEMIC RESPONSE

If the initial injury or insult is severe enough, the proinflammatory and anti-inflammatory mediators can appear in the systemic circulation. This may occur by direct entry into the bloodstream in the case of massive trauma, by spillover from the local site in the event of a severe infection, or by other means. The presence of these mediators in the general circulation is a sign that the local region is incapable of handling the situation and that assistance is needed. The proinflammatory response brings additional neutrophils, platelets, lymphocytes, coagulation factors, and other materials to the local site. This should eventually lead to a compensatory anti-inflammatory response that down regulates and controls the proinflammatory actions. In the typical situation, this will occur and no significant untoward effects are seen [26].

THIRD PHASE: PROINFLAMMATORY EXCESS

In some patients, control of the proinflammatory process does not occur, and there is a systemic reaction that can include hypotension, tachycardia, and abnormal body temperature. These are the early findings of SIRS and are thought to be due to: increased microvascular permeability with transudation into organs; platelet sludging, causing capillary blockage and ischemia; reper-

fusion injury; dysregulation of vasodilatory and vasoconstrictive mechanisms; and maldistribution of blood flow. Frequently, severe shock will follow, and unless homeostasis is restored, it can lead to organ dysfunction or organ failure. In addition, an overwhelming infection can occur secondary to an imbalance in the amount or effectiveness of proinflammatory and anti-inflammatory mediators [26].

FOURTH PHASE: EXCESSIVE IMMUNOSUPPRESSIVE RESPONSE

In some patients who survive an initial massive infection or other inflammatory process, there may be a compensatory, but excessive, anti-inflammatory response that results in immunosuppression [40]. This may explain the increased susceptibility to infection in patients with severe burns, trauma, hemorrhage, or pancreatitis. The process is thought to involve impaired monocyte function, altered T- and B-cell activity, diminished proinflammatory cytokines, and several other factors. This process can be self-limiting, and the immunosuppression can resolve without further consequences. If it does not resolve, patients may experience the final, life-threatening complication of MODS [26].

FIFTH PHASE: TRANSITION TO MODS

This phase indicates that there has been an overwhelming and inappropriate bodily response to the biological insult. It can take varied forms, including persistently elevated levels of proinflammatory mediators, whereby mortality is due to overwhelming inflammation and organ failure. This has been found in patients with SIRS and MODS. In other patients, persistent immunosuppression causes immunologic problems and increases the risk of mortality. If the immune system cannot recover, organ failure and death may follow. In another group of patients, there may be an oscillating effect, with periods of severe inflammation, immunosuppression, and then another proinflammatory response, resulting in increased mortality rates. This has been seen in severe burn patients, whose levels of cytokines fluctuate widely for several weeks after injury [26; 38].

The nature of the insult can significantly affect the degree of local inflammation and tissue injury. The balance between the expression of pro- and anti-inflammatory mediators often determines the magnitude of early tissue injury and risk of subsequent infectious complications. High levels of the proinflammatory mediators can initiate remote organ injury as a result of organ cross talk. Organ failure and death will occur in patients in phase five unless homeostasis can be maintained and there is a balance between pro- and anti-inflammatory forces [26; 41; 42].

PATHOPHYSIOLOGY OF SEPSIS

A complex, dynamic, and bidirectional interaction occurs between pathogens and the body's immune defense mechanisms during the course of invasive infection. If the defenses are breached successfully, the result can be severe sepsis [43].

As noted, in the United States, the infectious etiology of sepsis has shifted from a predominance of gram-negative bacteria to a predominance of gram-positive, drug-resistant pathogens [25]. This shift has led to a re-evaluation of basic assumptions about the pathogenesis of sepsis (e.g., there may or may not be differences in the host response to gram-negative organisms compared with the response to gram-positive organisms) [44; 45]. It is important to note that discrimination between gram-negative and gram-positive organisms is based on the recovery of specific pathogens from blood or the presumed site of infection rather than from any specific immunological criterion. In 30% to 50% of sepsis cases, the inciting organism is not identified [18; 25].

MICROBE RECOGNITION

The innate immune system recognizes invading pathogens and initiates an inflammatory or septic response. Gram-positive and gram-negative bacteria activate the immune response through unique cellular constituents referred to as pattern-associated molecular patterns (PAMPs) or microbial-associated molecular patterns (because they are

also common in nonpathogenic bacteria). PAMPs bind to immune system receptors called pattern recognition receptors (PRRs), which are expressed on the surface of host cells. PRRs are essential for initiating the host's immune response and regulating the adaptive immune response to infection or tissue injury, yet PRRs can also contribute to harmful systemic inflammation and tissue damage in organs [5; 25].

Toll-like receptors (TLRs) are the most common class of PRRs. Each of the known TLRs has unique binding properties that allow for the differentiation between gram-negative and gram-positive bacteria. When the TLR system recognizes a pathogen, a response is generated that is both generalized (similar response to dissimilar stimuli) and specific (pathogen is recognized by multiple TLRs simultaneously). The result is an immune system response that is tailored to the pathogen [25; 46]. The degree to which TLRs mediate the outcome of sepsis in individual patients is not yet fully understood [5].

TLRs can detect danger signals both inside and outside the cell [25]. TLRs induce the production of inflammasomes (multiprotein complexes) in response to the products of bacteria and damaged cells. This in turn activates caspase-1, which is important in the process of inflammation and apoptosis (a counter-regulator of the initial inflammatory response in sepsis). Caspase-1 activation is considered to be a prerequisite for an adequate immune response. Like other proinflammatory products, caspase-1 can have both positive and negative effects on the course and outcome of sepsis [5].

Nod-like receptors (NLRs) are a less well understood class of PRRs. NLRs can detect danger elements (e.g., microbial motifs, live bacteria, host-derived molecules) inside the cell [25].

ENDOTOXINS AND OTHER BACTERIAL TOXINS

Endotoxin was identified more than 100 years ago, but its potential role in the development of sepsis was not identified until 1951. Experimental studies using endotoxin reproduced some of the features of septic shock in animals, but they did not represent the features of septic shock characteristic to humans. Evidence that endotoxin might play a pathogenic role in humans was discovered accidentally in 1991, but its precise role in sepsis remains elusive. Endotoxin is often found in the blood of critically ill patients, making its measurement of limited diagnostic value. In addition, other bacterial toxins (e.g., gram-positive peptidoglycans) can induce the production of mediators associated with sepsis [18].

COAGULATION SYSTEM

The coagulation system plays an important role in the sepsis-induced inflammatory cascade. Coagulation is the inflammatory reaction to tissue injury and is activated independent of the type of microbe (e.g., gram-positive and gram-negative bacteria, viruses, fungi, or parasites). Coagulation contributes to the outcome in sepsis by down regulating fibrinolysis and the anticoagulant systems. The collaboration between clotting and inflammation, which works to wall off damaged and infected tissues, is an important host survival strategy. Coagulation induced by inflammation can in turn contribute to further inflammation. A key to determining survival in sepsis is to limit the damage while retaining the benefits of localized clotting and controlled clearance of pathogens [5; 14; 47].

A continuum of coagulopathy in sepsis has been suggested, extending from the appearance of coagulation abnormalities prior to the onset of any clinical signs of severe sepsis to consumption of anticoagulant proteins and suppression of the fibrinolytic system. Depletion of anticoagulant and fibrinolytic factors contributes to the microvascular deposition of fibrin that is associated with organ dysfunction. Coagulation abnormalities in sepsis contribute significantly to organ dysfunction and death [5; 14; 48].

MANIFESTATIONS OF SEPSIS

Any septic patient who has evidence of dysfunction in one organ in the absence of an obvious cause such as traumatic injury may have incipient dysfunction of other organs. The manifestations of sepsis may be seen in the cardiovascular, pulmonary, central nervous, renal, gastrointestinal, and hematologic systems of the body (most frequently in the lungs and circulatory system) [48].

The following signs and symptoms should not be thought of merely as the manifestations of sepsis but as clear evidence that MODS may be developing. The host response may be more important in the genesis of MODS than the specific bacterium, virus, or traumatic injury. In most patients, the extent of systemic changes corresponds to the extent of shock [19; 49; 50].

CARDIOVASCULAR

In addition to hypotension, a variety of other cardiovascular manifestations may be seen. Tachycardia is common. In addition, the left and right ventricles are dilated, ejection fractions are often depressed, and the Frank-Starling and diastolic pressure-volume relationships are altered [50; 51].

Before the onset of shock, the patient's condition is usually hyperdynamic. The skin is warm and flushed, pulse volume is increased, and pulse pressure is wide. Cardiac output is typically elevated, and systemic vascular resistance (SVR) is usually

decreased. Despite the increase in cardiac output, serum lactate levels are often elevated. Anaerobic metabolism occurs because of inadequate nutrient blood flow [50; 52].

As shock sets in, SVR drops precipitously, although cardiac output continues to increase. In the later phases of shock cardiac output declines, which exacerbates the effects of hypoperfusion and allows lactate to accumulate. The decrease in cardiac output can result in a subsequent elevation of the SVR [1; 19; 49; 50; 52].

PULMONARY

Tachypnea, with a respiratory rate of more than 20 breaths per minute, is often the earliest pulmonary sign of sepsis, occurring before hypoxemia. Hypoxemia is usually present, although it may be masked by hyperventilation. The cause of hypoxemia is usually ventilation-perfusion mismatch.

As sepsis continues, marked respiratory alkalosis often ensues; PaCO₂ may be 30 mm Hg or less. The hypoxemia progresses rapidly. The result is often pulmonary edema and respiratory failure. Other pulmonary manifestations of sepsis include respiratory muscle dysfunction and bronchoconstriction. The onset of either acute respiratory distress syndrome (ARDS) or persistent pulmonary hypertension is an ominous sign [19; 49; 50].

CENTRAL NERVOUS SYSTEM


Altered mental status may be the most common and most overlooked manifestation of sepsis. This causes elderly patients to be at particularly high risk. Early changes include withdrawal, confusion, irritability, or agitation. In patients with severe infection, one may see disorientation, lethargy, seizures, or frank obtundation [49; 50].

Eventually, symptoms and signs of encephalopathy, including nonfocal neurologic manifestations, may be seen, and some patients may become comatose. In addition, evidence of polyneuropathy, including impaired deep tendon reflexes, muscle weakness, and wasting, may be present [19; 49; 50].

Patients with sepsis and encephalopathy are more likely to be bacteremic and have concomitant renal and hepatic dysfunction than are patients with sepsis and normal mental status. Furthermore, the risk of death increases as the encephalopathy worsens [50].

RENAL

The renal manifestations of sepsis include oliguria and azotemia. Urinary sediment may contain red blood cells, casts, and protein. The urinary excretion of sodium may be markedly reduced (less than 20 mEq/L), and urinary osmolality may be increased (greater than 450 mOsm/kg). Protracted oliguria may lead to acute tubular necrosis or renal failure [19; 49].



The Society of Critical Care Medicine guideline committee suggests the use of continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients.

(http://www.guidelines.gov/summary/summary.aspx?doc_id=12231. Last accessed May 8, 2009.)

Strength of Recommendation/Level of Evidence: 2D
(A weak recommendation based on case series or expert opinion)

GASTROINTESTINAL

Impaired motility is the most common gastrointestinal problem. Often, this manifests as abnormal gastric emptying or as a dynamic ileus. Stress ulceration is another common problem, although it may be seen less often now than in the past. There is some evidence that stress ulcers are less likely to develop when patients are given adequate fluid resuscitation, although this has not been proven conclusively [53].

HEPATIC

Large but transient elevations in serum transaminase levels may follow an episode of severe shock or hypoxemia. Less severe increases, often in association with mild-to-moderate hyperbilirubinemia, suggest focal hepatic necrosis. In the final states of sepsis, patients may have evidence of frank hepatic insufficiency, including hypoprothrombinemia, jaundice, lactic acidosis, and hypoglycemia [2; 49; 50].

HEMATOLOGIC

Leukocytosis, usually accompanied by a shift to the left, is the most common hematologic manifestation of sepsis. Multifactorial anemia is common in late-stage sepsis. Decreased maturity and/or survival of red blood cells may contribute to anemia. Thrombocytopenia and coagulation abnormalities (elevated prothrombin or partial thromboplastin times) are often seen in sepsis. Thrombocytopenia is more common than overt disseminated intravascular coagulation (DIC) in sepsis. When DIC is present, the outlook is poor [2; 17; 49; 54; 55].

DIAGNOSIS AND MANAGEMENT

Methods to identify critically ill patients who are likely to die as a result of sepsis have become clearer, and increased awareness that sepsis is more common and lethal than previously understood has helped to promote the development of an organized approach to care. While the early diagnosis of sepsis continues to be a challenge (primarily because a rapid, sensitive, and specific diagnostic test is lacking), research indicates that improvements in outcomes are possible when treatment protocols are applied in a timely manner [48].

In 2008, in an attempt to standardize and improve the care of patients with severe sepsis and septic shock, SCCM updated its previously published guidelines. The guidelines articulate several points of care for the management and support of patients with severe sepsis. The points of care are outlined in the following sections [53].

MANAGEMENT OF SEVERE SEPSIS

Initial Resuscitation and Diagnosis

The SCCM guidelines recommend the resuscitation of a patient with sepsis-induced shock (defined as tissue hypoperfusion) as soon as the hypoperfusion is recognized (i.e., not delayed pending admission to an intensive care unit [ICU]). They also stress that this be included in facility protocols. During the first 6 hours of resuscitation, the treatment goals should include [53; 56]:

- Central venous pressure of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients)
- Mean arterial pressure of 65 mm Hg or greater
- Urine output of 0.5 mL/kg/hour or greater
- Central venous or mixed venous oxygen saturation of at least 70% or 65%, respectively

The SCCM recommends obtaining appropriate cultures before beginning antibiotic therapy, assuming that obtaining the cultures will not adversely delay antibiotic administration. Obtaining at least two cultures is recommended: one drawn percutaneously and one drawn through vascular access devices (if the devices were inserted within the last 48 hours). Cultures from other suspected sites should be obtained as well. The guideline committee also recommends that imaging studies be performed to confirm the source of infection, assuming the patient's condition allows it [53].

Antibiotic Therapy and Source Control

Antibiotic therapy should be started as early as possible, ideally within the first hour of recognition of severe sepsis or septic shock. The initial choice of antibiotics will depend on the most likely pathogens associated with the source of infection as well as the prevalent microorganisms in the local community and hospitals. The susceptibility of the pathogen and the ability of the antibiotic to penetrate to the source of the infection must also be considered. A combination of drugs with

activity against all likely pathogens should be administered initially, but the regimen should be reassessed daily. The goal should be to find a single, narrow-spectrum antibiotic that will control the infection [53; 57]. It has been found that combining a beta-lactam antibiotic (e.g., penicillins, cephalosporins) with an aminoglycoside (e.g., gentamycin) was no more effective in reducing mortality than using the beta-lactam agent alone. In addition, the combination carries an increased risk of renal damage [53; 57].

In the event that the syndrome is due to something other than an infectious cause, such as trauma, the antibiotics should be discontinued as soon as possible. In general, the therapy should continue for 7 to 10 days [53; 57].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The Society of Critical Care Medicine guideline committee recommends that the duration of antimicrobial therapy in sepsis patients typically be 7 to 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, or who have immunologic deficiencies including neutropenia.

(http://www.guidelines.gov/summary/summary.aspx?doc_id=12231. Last accessed May 8, 2009.)

Strength of Recommendation/Level of Evidence: 1D
(A strong recommendation based on case series or expert opinion)

Source control includes direct intervention at the site of the infection. The SCCM recommends that a diagnosis of infection be sought and confirmed or excluded as quickly as possible within the first 6 hours of presentation. Source control could be the draining of an infected cyst or abscess, debridement of infected tissue, or removal of an infected device or catheter (removal should be prompt after other vascular access has been established). Rather than performing a major surgical procedure, which could result in greater morbidity or death, more simple percutaneous or radiological procedures should be considered [53].

Fluid Therapy

The immediate and vigorous administration of fluids is recommended, as long as hemodynamic improvement continues. The use of either isotonic crystalloids (a minimum of 1000 mL over 30 minutes) or iso-oncotic colloids (300–500 mL over 30 minutes) to reverse tissue hypoperfusion and lactic acidosis is recommended. Fluid resuscitation should initially target a CVP of at least 8 mm Hg (or 12 mm Hg in patients who are mechanically ventilated) [53].

Vasopressors and Inotropic Therapy

Vasopressors may be required to restore adequate blood pressure and perfusion. Norepinephrine or dopamine (administered through a central catheter as soon as placement is possible) are considered first-choice vasopressor agents to correct hypotension in septic shock [53]. Norepinephrine appears to be more effective at reversing hypotension than dopamine, but there are concerns that many of the biological effects of dopamine might cause harm to patients in septic shock. Low-dose dopamine should not be used for renal protection [53; 56].

If these agents do not provide the desired result (i.e., mean arterial pressure of 65 mm Hg or greater), vasopressin may be added to the norepinephrine and administered at an infusion rate of 0.03 units/min [53]. Vasopressin should not be administered as the initial agent in septic shock. Phenylephrine can also be used to increase blood pressure, especially if a tachyarrhythmia is present, but should not be administered as the initial vasopressor. Intravenous preparations should be administered only by properly trained individuals familiar with its use [53; 56; 66].

Inotropic therapy may involve the use of dobutamine if the cardiac output remains low. If dobutamine is used, it should be combined with the vasopressors. All patients requiring vasopressors should have an arterial line placed as soon as practically possible [53; 56].

Corticosteroids

Prior to the 1990s, there was evidence that the overall 28-day mortality was not impacted by the use of corticosteroids; consequently, their use was not advised. A review of studies conducted between 1992 and 2003 concluded that corticosteroids did not change the 28-day mortality in patients with severe sepsis and septic shock, but that the use of low-dose corticosteroids did reduce the all-cause mortality [58].

The SCCM guidelines suggest that IV hydrocortisone be given only to adult patients in septic shock who are poorly responsive to vasopressor therapy and fluid replacement. Doses of hydrocortisone should not exceed 300 mg/day and are not recommended for use in severe sepsis or septic shock [53]. The addition of 50 mcg/day of fludrocortisone is suggested if hydrocortisone is not available. Corticosteroids should be stopped or tapered off after the resolution of septic shock unless the patient's history warrants maintenance therapy or the use of stress doses [53; 58].

Recombinant Human Activated Protein C

Drotrecogin alpha (activated), or recombinant human activated protein C (rhAPC), has been studied in patients with severe sepsis due to its anti-thrombotic, anti-inflammatory, and profibrinolytic properties. It has been found to reduce mortality but also has been associated with increased bleeding [59].

In 2005, the European Medicines Evaluation Agency (EMA) recommended that drotrecogin alpha (activated) should only be used in instances of multiple organ failure and administered by experienced specialists in institutions familiar with treating advanced sepsis. The EMA recommendations state that it should only be used in high-risk patients when therapy can be initiated within 24 hours of the onset of organ failure [60]. It is not recommended for patients with single organ dysfunction and low risk of death, especially if they have had surgery within the past 30 days [53; 60; 61].

Blood Product Administration

In some cases, blood product administration may be required, especially if the hemoglobin falls below 7.0 g/L. In patients with severe sepsis, a platelet transfusion is suggested if the platelet count is less than 5000/mm³, regardless of apparent bleeding, and it may be considered if the count is between 5000/mm³ and 30,000/mm³ and there is significant risk of bleeding. Patients who require surgery typically require a platelet count that is in excess of 50,000/mm³ [53].

The routine use of erythropoietin is not recommended for treatment of anemia in patients with severe sepsis unless other conditions are present, such as the compromise of red blood cell production induced by renal failure. In addition, the routine use of fresh frozen plasma is not recommended unless there is active bleeding or planned surgery. Direct administration of antithrombin agents for the treatment of severe sepsis or septic shock is not advised [53].

SUPPORTIVE THERAPY FOR SEVERE SEPSIS

Mechanical Ventilation

Patients who develop sepsis-induced acute lung injury (ALI) or ARDS may require assisted ventilation. The routine use of pulmonary artery catheters for patients with ALI/ARDS is not recommended, and it is important to remember to avoid high pressures and volumes. The SCCM guideline committee recommends that the maximum end-inspiratory plateau pressures remain at or below 30 cm H₂O and that tidal volumes start at 6 ml/kg of predicted body weight. The committee also recommends titrating the positive end-expiratory pressure according to bedside thoracopulmonary compliance [53].

Unless contraindicated, the guideline committee recommends that mechanically ventilated patients be kept with the head of the bed elevated (30–45 degrees is suggested) to limit aspiration and prevent the development of ventilator-associated

pneumonia. In hospitals with advanced experience and equipment, it may be advantageous to treat patients with ARDS in a prone position if higher pressures are required and the patient's condition allows for the positional change [53].

A protocol for weaning patients from the ventilator should be developed for use following a successful spontaneous breathing trial. Extubation should be considered if the breathing trial is successful. A successful breathing trial is characterized by the following criteria [53]:

- Patient is arousable.
- Patient is hemodynamically stable (without vasopressor agents).
- Patient has developed no new potentially serious conditions.
- Ventilatory and end-expiratory pressure requirements are low.
- Fraction of inspired oxygen requirements are able to be safely delivered with a face mask or nasal cannula.

The SCCM recommends a conservative fluid strategy for patients with ALI and no evidence of tissue hypoperfusion in order to decrease the days of mechanical ventilation and length of ICU stay [53].

Sedation, Analgesia, and Neuromuscular Blockade

Sedation, whether intermittent or by continuous infusion, may be required for patients who are mechanically ventilated. The SCCM guideline committee recommends that daily interruption or lightening of the sedation be accomplished and a protocol established to maintain the minimum degree of sedation. Neuromuscular blockers should be avoided due to the risk of continued blockade in septic patients after the drugs are discontinued. If the drugs must be used for the first hours of mechanical ventilation, an intermittent bolus or continuous infusion with close monitoring is recommended [53].

Glucose Control

Glucose control includes a regimen of appropriate nutrition, usually administered parenterally. Following initial stabilization, patients with severe sepsis and hyperglycemia should receive IV insulin therapy to reduce blood glucose levels. Blood glucose should be maintained at or less than 150 mg/dL. Some studies suggest that a continuous infusion of glucose and insulin be instituted, with regular monitoring every 1 to 2 hours, and then every 4 hours after the baseline level has been accomplished. Low glucose levels should be interpreted with caution [53; 56].

Bicarbonate Therapy and Deep Vein Thrombosis Prophylaxis

Bicarbonate therapy to improve hemodynamics or reduce vasopressor requirements is not recommended for the treatment of patients with a pH equal to or greater than 7.15 [53]. The use of bicarbonates in SIRS requires additional study.

In contrast, the use of anticoagulants to prevent deep vein thrombosis (DVT) has been well studied. For patients with severe sepsis, the SCCM guideline committee recommends the administration of low-dose unfractionated heparin (UFH), 2 to 3 times per day, or low-molecular-weight heparin (LMWH), once daily, unless there are contraindications, such as active bleeding, thrombocytopenia, or severe coagulopathy. LMWH has been found to be superior to UFH in high-risk patients [53].

When contraindications exist, other preventive measures, such as graduated compression stockings or an intermittent compression device, are recommended. In very high-risk patients, such as those who have severe sepsis and a history of DVT, trauma, or orthopedic surgery, a combination of both therapies is suggested [53; 56].

Stress Ulcer Prophylaxis

The SCCM guideline committee recommends stress ulcer prophylaxis in patients with severe sepsis in order to prevent upper gastrointestinal bleeding. Stress ulcer prophylaxis involves the administration of H₂ receptor inhibitors (which have been shown to be more effective than sucralfate) or proton pump inhibitors. The potential for development of ventilator-associated pneumonia (as a result of increased stomach pH) should be weighed against the benefit of preventing upper gastrointestinal bleed [53].

Communication

Also included in the supportive therapy points of care is the SCCM recommendation that advance care planning, including the communication of likely outcomes and realistic goals of treatment, be discussed with patients and families [53]. As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because communication with patients and families is considered an essential aspect of care, it is each practitioner's responsibility to ensure that information regarding goals and potential outcomes are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

PEDIATRIC CONSIDERATIONS

In 2002, an international panel of experts met to revise the definitions of severe sepsis and septic shock to include and reflect the developmental stages of children and age-specific norms of vital sign and laboratory data. The panel also modified the adult criteria for SIRS and proposed dividing the pediatric population into the following six distinct age groups to account for age-specific risks [62]:

- Newborn: 0 days to 1 week of age
- Neonate: 1 week to 1 month of age
- Infant: 1 month to 1 year of age
- Toddler and preschool: 2 to 5 years of age
- School-age child: 6 to 12 years of age
- Adolescent and young adult: 13 to 17 years of age

The panel's definition of SIRS for children includes the presence of at least two of the following criteria (one of which must be abnormal temperature or leukocyte count) [62]:

- Core temperature greater than 38.5°C or less than 36°C (measured by rectal, bladder, oral, or central catheter probe). Hypothermia may indicate serious infection (especially in infants).
- Tachycardia greater than 2 standard deviations above normal for the child's age in the absence of external stimulus; or unexplained persistent elevation over a 4-hour time period; or, for children younger than 1 year of age, bradycardia (as defined by the panel); or unexplained persistent depression over a 30-minute time period. Bradycardia is not a sign of SIRS in older children but may be a sign in the newborn.
- Mean respiratory rate greater than 2 standard deviations above normal for the child's age or mechanical ventilation

- Leukocyte count that is either elevated or depressed for the child's age; or greater than 10% immature neutrophils

Because many pediatric disease processes present with symptoms of tachycardia and tachypnea, a diagnosis of SIRS should not be based solely on elevated heart and respiratory rates; abnormalities in temperature or leukocyte count must be present. Biomechanical markers of inflammation (e.g., elevated sedimentation rate, C-reactive protein, interleukin-6) have not been proven specific enough to be included in the diagnostic criteria [62].

The following definitions have also been proposed for use in the pediatric population [62]:

- Sepsis: SIRS in the presence of or as a result of suspected or proven infection
- Severe sepsis: sepsis plus cardiovascular organ dysfunction, ARDS, or 2 or more other organ dysfunctions (as defined by specific criteria)
- Septic shock: sepsis plus cardiovascular organ dysfunction

The administration of antibiotics within 1 hour of the identification of severe sepsis (after obtaining appropriate cultures) is recommended [53].

The diagnosis of septic shock in neonates and children should be suspected when the usual inflammatory triad of fever, tachycardia, and vasodilation is accompanied by mental changes. This may be manifested as inability to be aroused, inconsolable irritability, or lack of interaction with parents. Children may present with hyper- or hypothermia, signs of decreased perfusion, and/or decreased urinary output. Because children often maintain their blood pressure until they are severely ill, hypotension is not necessary for the diagnosis (as in adults), but if present, it helps confirm a suspected case of septic shock. It is also important to note that shock in children may occur long before hypotension occurs [7; 62].

There are two classes of septic shock. In hyperdynamic shock, the child has rapid capillary refill and bounding pulses. In hypodynamic shock, there is prolonged capillary refill, mottled cool extremities, and diminished pulses. In both types, immediate resuscitation involves maintaining necessary circulation with fluid replacement, assuring proper ventilation, and maintaining threshold heart rates. Suggested therapeutic end points include a capillary refill of less than 2 seconds, warm extremities, urine output greater than 1 mL/kg/hr, normal blood pressure, normal mental status, and normal pulses with no differential between peripheral and central pulses. Frequent monitoring is required as rapid changes may occur in the status of a child with sepsis [53; 63].

The international consensus panel also developed criteria for MODS in the pediatric population based on scoring systems previously described in the literature. These systems include the Pediatric Logistic Organ Dysfunction score, Pediatric MODS score, and Multiple Organ System Failure score. The panel also considered the criteria used in the open-label rhAPC study in their development of criteria for pediatric MODS [62].

The panel's goal was to identify criteria that would optimize the enrollment of children with severe sepsis in clinical studies. To that end, they specified the following [62]:

- Cardiovascular and respiratory organ dysfunction must be present (and mechanical ventilator support for respiratory failure, if used).
- Other organ dysfunctions should be monitored during clinical studies.

- The usefulness of organ dysfunction-free days as a primary end point should be confirmed.
- Documenting organ dysfunction should be achieved with a pediatric MODS scoring system.

Experts generally agree that additional evidence-based studies are needed to understand and accurately define pediatric sepsis by accounting for the physiologic variables, age-specific norms, and risk factors of this population [63; 64].

CONCLUSION

Severe sepsis and septic shock present the clinician with a difficult management situation. Patients are usually unstable and may rapidly progress to ARDS, MODS, and death. There are several possible causes of sepsis, including traumatic injury, infections, and burns. Gram-negative and gram-positive organisms associated with nosocomial infections account for many cases. Other bacteria, viruses, fungi, and noninfectious etiologies account for the remaining [17; 19]. The mortality rate from sepsis is approximately 30%, and it was the tenth leading cause of death in the U.S. in 2005 [23; 65].

The pathophysiology of sepsis involves multiple organ systems and is often related to an abnormal proinflammatory and/or anti-inflammatory response to a bodily insult. Management includes proper antibiotic treatment plus maintenance of hydration, ventilation, and overall homeostasis.

Evidence-based practice guidelines are available to assist in the diagnosis and treatment of these disorders. This course outlines some of the current recommendations and suggestions provided by the SCCM and other experts experienced in treating patients with these disorders.

CASE STUDY

Patient A is a woman, 50 years of age, who was admitted to the emergency department after a motor vehicle accident. She incurred massive abdominal injuries and was transported to the emergency department unconscious and hypotensive upon arrival. She was receiving 35% O₂ via oxygen mask. Her respiratory rate was 28 breaths per minute, and lung sounds were clear bilaterally. She had a sinus tachycardia with a heart rate of 150 beats per minute. Her blood pressure was 80/45 mm Hg. The patient had a 40 pack-year history of cigarette smoking and had been taking medications to control hypertension.

She was transported via stretcher to radiology for a computed tomography scan, which revealed bleeding in the peritoneum. She was taken immediately to surgery. Following surgery, she was taken to the ICU. Three liters of Ringer's lactate had been infused in surgery. Estimated blood loss was 2500 cc, and she received 6 units of whole blood in surgery. Despite fluid resuscitation, the patient was hypotensive during much of the surgical procedure. To assess fluid management, a pulmonary artery catheter was placed while in surgery. A variety of data were obtained upon arrival to the surgical ICU.

Vital Signs	Hemodynamic Parameters	Arterial Blood Gases (ABGs)	Laboratory Values	Ventilator Settings
BP: 100/50 mm Hg Pulse: 120 beats per minute Respirations: 14 breaths per minute on respirator Temperature: 96.5°F	CVP: 5 mm Hg PAP: 25/15 mm Hg PAWP: 13 mm Hg CO: 3.2 SVR: 1100 SvO ₂ : 72%	pH: 7.45 PaCO ₂ : 36 PO ₂ : 80 HCO ₃ : 28 SaO ₂ : 95%	Sodium: 130 Potassium: 4.5 Chloride: 95 Glucose: 140 Hemoglobin: 11.5 Hemocrit: 35 WBC: 11,000	Rate: 14 on assist control FiO ₂ : 40% Tidal Volume: 800
BP: blood pressure; CI: cardiac index; CO: cardiac output; CVP: central venous pressure; HCO ₃ : bicarbonate; FiO ₂ : fraction of inspired oxygen; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PO ₂ : partial pressure of oxygen; SaO ₂ : oxygen saturation; SvO ₂ : venous oxygen saturation; SVR: systemic vascular resistance; WBC: white blood cells.				

Patient A was hemodynamically stable following surgery. She awakened slowly and was able to be extubated and put on a 40% O₂ mask.

POST-OPERATIVE DAY 3

Three days after surgery, the patient's level of consciousness began to deteriorate. She was obtunded and only awoke when her name was called. Her skin was warm to touch and appeared flushed, and she had 4+ bounding pulses.

Vital Signs	Hemodynamic Parameters	ABGs on 40% O ₂ Mask	Laboratory Values
BP: 110/72 mm Hg Pulse: 118 beats per minute Respirations: 28 breaths per minute Temperature: 104°F	CVP: 6 mm Hg PAP: 20/12 mm Hg PAWP: 10 mm Hg CO: 6.0 CI: 4.2 SVR: 850 SvO ₂ : 85%	pH: 7.48 PaCO ₂ : 30 PO ₂ : 85 SvO ₂ : 85%	Hemoglobin: 9.8 Hemocrit: 28.8 WBC: 25,000 Platelets: 168,000

Urine output was 15 cc per hour for the last 3 hours. Cultures of sputum, urine, and blood were obtained. Antibiotic therapy was initiated.

Analysis

1. Identify the term that best describes Patient A's condition at the present moment.

Sepsis is caused by bacteria, viruses, or fungi in the blood. It is a clinical continuum ranging from bacteremia through septicemia to septic shock. Patient A is presently displaying signs of septicemia. Her blood pressure and cardiac output are within an acceptable range. Chemical mediators are being released and causing the physiologic changes.

POST-OPERATIVE DAY 5

On the 5th post-operative day, Patient A's blood pressure dropped to 84/58 mm Hg; her respirations were 32 breaths per minute, heart rate was 130 beats per minute, and temperature was 97°F. Despite 3000 cc fluid resuscitation, Patient A's condition continued to deteriorate. She was reintubated and connected to a respirator.

Hemodynamic Parameters
CVP: 3 mm Hg
PAP: 15/7 mm Hg
PAWP: 5 mm Hg
CO: 3.0
CI: 1.6
SVR: 1597
SvO ₂ : 68%

Analysis

1. List the risk factors applicable to Patient A's case.

Trauma

Cigarette smoking

Hypertension

Abdominal injuries

Multiple invasive lines

Surgery

2. Patient A is in what stage of septic shock? Describe the symptoms to support your answer.

Patient A is in the hypodynamic (cold) phase of septic shock. This phase is characterized by decreased cardiac output, increased SVR, hypotension, and inadequate tissue perfusion.

3. What are some of the causative organisms associated with sepsis?

Escherichia coli

Klebsiella

Enterobacter

Pseudomonas aeruginosa

Staphylococcus aureus

POST-OPERATIVE DAY 8

On post-operative day 8, Patient A's skin was cool and cyanotic, and mottling was noted in the extremities. She responded only to painful stimuli.

Vital Signs	Hemodynamic Parameters	ABGs	Laboratory Values
BP: 38/40 mm Hg Pulse: 170 beats per minute Respirations: 14 breaths per minute on respirator. She is not assisting. Temperature: 95.6°F	CVP: 6 mm Hg PAP: 38/20 mm Hg PAWP: 18 mm Hg CO: 2.0 SVR: 1746 SvO ₂ : 48%	pH: 7.28 PaCO ₂ : 48 PO ₂ : 40 SvO ₂ : 52% SaO ₂ : 80%	Sodium: 160 Potassium: 6.8 BUN: 48 Creatinine: 3.0 Platelets: 72,000 PT: 21 PTT: 100.5
BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time.			

Analysis

1. Patient A's temperature is 95.6°F. Is this to be expected in the hypodynamic phase and why?
Yes. Hypothermia is common during the hypodynamic phase. Metabolic and myocardial activity are greatly reduced.
2. What is the physiologic cause of increased SVR in the hypodynamic phase?
In the hypodynamic phase, SVR is caused by decreased cardiac output and elevated serum lactate levels.
3. What management would be appropriate in this phase?
Afterload reduction and myocardial support are of great importance at this point. Before the use of vasodilators, cautious fluid administration with hemodynamic monitoring is essential to provide normovolemia as the vascular capacitance increases. If fluid resuscitation proves unsuccessful, the use of vasodilators in combination with a positive inotrope may be attempted.

POST-OPERATIVE DAY 12

Patient A died on the 12th post-operative day due to the complications of septic shock: renal failure and hepatic failure complicated by DIC and ARDS.

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