Infectious Emergencies in Critically Ill Patients: Postsplenectomy Infection, Necrotizing Fasciitis, Sepsis

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INTRODUCTION

Medical and surgical emergencies involving infections place patients at high risk for morbidity and mortality while often presenting a diagnostic and therapeutic challenge to clinicians caring for critically ill patients. Infectious emergencies that arise because of the anatomic site of involvement (eg, the central nervous system, eye, cardiovascular system, upper airway) can lead to rapid localized fulmination and a poor prognosis, if untreated. Bacteremia, sepsis, and toxin-mediated infections (eg, toxic shock syndrome) also constitute infectious emergencies requiring prompt intervention with antibiotic therapy and other supportive management to avoid rapid multisystem dysfunction. Immunocompromised hosts are particularly susceptible to infections resulting in medical emergencies. Moreover, atypical presentations and rare or resistant organisms can create a clinical course in which the infectious emergency goes unrecognized.1–3

Severe infections that constitute medical emergencies, including meningitis, epiglottitis, and neutropenic fever, necessitate rapid intervention with parenteral antibiotics soon after their presentation. In addition, many infectious emergencies, such as intraocular eye infection and epidural abscess, require prompt subspecialty surgical evaluation for definitive diagnosis and treatment.

This review focuses on 3 specific infectious diseases constituting medical emergencies seen in the intensive care unit (ICU)—postsplenectomy infection, necrotizing fasciitis (NF), and sepsis—using a case-based approach to illustrate important points.

POSTSPLENECTOMY INFECTION

CASE 1 PRESENTATION

A 30-year-old man who had a splenectomy 2 years ago comes to the emergency department (ED) reporting fever (temperature to 38.6°C [101.5°F]), headache, vomiting, and 3 episodes of loose stools. He received appropriate vaccinations (ie, pneumococcal, meningococcal, and Haemophilus influenzae type b [Hib]) preoperatively. He has not taken any antibiotic prophylaxis since the splenectomy. His condition deteriorates in the ED with hypotension, and he is transferred to the ICU.

What is the most appropriate work-up and management of this patient’s current condition?

OVERWHELMING POSTSPLENECTOMY INFECTION

General Considerations

Overwhelming postsplenectomy infection (OPSI), also known as postsplenectomy sepsis syndrome, is considered a major medical emergency with death rates in patients who have undergone splenectomy as much as 600 times greater than those in the general population.4 Fulminant, potentially life-threatening infection represents a major long-term risk after splenectomy. One reason is that, besides its other functions, the spleen plays a role in the phagocytosis and clearance of any unopsonized particulate matter, in the development of specific immune responses (including IgM production), and in the production and processing of opsonins. Consequently, splenectomized patients are at particular risk for infection with encapsulated bacteria.

Epidemiology

The precise incidence of OPSI remains controversial, and most published data antedate the widespread availability of pneumococcal and Hib vaccines. Children younger than 15 years have a greater risk for OPSI (8%) compared with adults (2%). The incidence and severity of OPSI is affected by underlying disease, as well as by patient age and the time interval since splenectomy. In trauma patients who undergo splenectomy, for example, the incidence of sepsis equals that of the general population but is 58 times more fatal.5
The frequent existence of splenic implants or accessory spleens in polytrauma patients is thought to be a contributing factor. Immune status is also an important variable.

The majority of cases of OPSI (50%–75%) occur within 2 years following splenectomy, but increased risk remains lifelong. The overall mortality for OPSI, according to older published studies, is 50% to 70%, but more recent information suggests that mortality is reduced to 10% when informed patients seek prompt medical attention.

**Etiology**

**Infectious organisms.** The most commonly implicated organisms in cases of OPSI are *Streptococcus pneumoniae, H. influenzae, Neisseria meningitidis*, and *Capnocytophaga canimorsus* (associated with dog bites). Less commonly, *Escherichia coli, Staphylococcus aureus*, group B streptococci, and *Pseudomonas* species can be responsible for the infection. Even more rarely, causative organisms can include *Enterococcus* species, *Bacteroides* species, *Salmonella* species, *Bartonella* species, *Plesiomonas shigelloides*, and *Eubacterium pleautii*. Pneumococcal infections account for the majority of reported cases of OPSI. However, *H. influenzae* infections are significant in children with this infection.

Bacterial proliferation in OPSI may be so extreme that bacteria are noted in buffy coat preparations or within neutrophils present on a peripheral blood smear. The splenectomized host also is more susceptible to intraerythrocytic protozoa, including *Babesia* and *Plasmodium* (malaria) species; in cases of infection with these organisms, a fulminant hemolytic febrile state can occur. In human cases of babesiosis, typically a mild illness in otherwise healthy adults, a significant percentage of the associated morbidity and mortality has occurred in asplenic hosts.

**Asplenia and hyposplenemia.** OPSI also has been associated with functional asplenia and hyposplenemia. Splenic dysfunction can occur as a result of a variety of gastrointestinal, immunologic, inflammatory, infiltrative, and hematologic diseases, many of which have been linked to individual case reports of OPSI. Asplenic children with sickle cell anemia or asplenic and hyposplenic heterozygotes for hemoglobin S or C are at especially high risk for OPSI. The identification of Howell-Jolly bodies on a peripheral blood film is suggestive of asplenia and hyposplenemia.

Bone marrow transplantation is a well-recognized cause of functional hyposplenism associated with an increased incidence of pneumococcal bacteremia and *H. influenzae* pneumonia. Typically, these infections occur 6 months after bone marrow transplantation, at the time when pneumocystis prophylaxis is stopped. Patients undergoing high-dose corticosteroid therapy or splenic irradiation as part of cancer therapy also may have decreased or abnormal splenic phagocytic function and an increased risk for OPSI.

**Clinical Manifestations**

Typical clinical manifestations of OPSI include an initial brief prodrome of fever and nonspecific symptoms (eg, headache, malaise, nausea, vomiting, diarrhea, chills, abdominal pain) that rapidly progress to overwhelming septic shock; disseminated intravascular coagulation and death often occur within 24 to 48 hours. Pneumonia and meningitis frequently accompany OPSI (in approximately 50% of cases). In many patients, however, there is no obvious site of bacterial colonization, and a cryptic source originating in the nasopharynx is postulated.

**Diagnosis**

Initial diagnosis relies on a high index of suspicion in any splenectomized patient with a febrile presentation. Diagnostic work-up should never delay initiation of empiric antibiotic therapy. Peripheral blood smears anduffy coat preparations are helpful in detecting the presence of bacteria. Cultures of blood, urine, and sputum should be performed routinely, and lumbar puncture should be strongly considered. Further tests should be guided by patient history.

**Management**

Broad-spectrum antibiotic therapy should be initiated promptly, to cover the potentially causative organisms (eg, *S. pneumoniae, H. influenzae, N. meningitidis*). Given the current possibility of penicillin-resistant pneumococci, a regimen of vancomycin plus ceftriaxone or similar combinations are likely to be appropriate, with additional coverage based on the clinical history and examination. Moreover, supportive management for any evidence of sepsis should be provided.

Preventive management includes education, immunoprophylaxis, and chemoprophylaxis (Table 1). Immunization with pneumococcal, meningococcal, and Hib vaccines should be performed, preferably at least 2 weeks prior to splenectomy or, if that time frame is not possible, soon after surgery. The overall efficacy of pneumococcal vaccination in preventing OPSI has never been adequately determined by objective study. Revaccination after 5 to 6 years is recommended for asplenic or functionally hyposplenic individuals but should occur sooner if there is reason to suspect a
Table 1. Preventive Management Guidelines for Asplenic or Hyposplenic Patients

Education
Patients should be informed about risks and types of infection and told to wear a medical alert bracelet or necklace and carry a wallet card indicating their condition.
Patients should be advised to seek prompt medical attention if unwell, if traveling to a malaria- or babesiosis-endemic area, or if bitten by ticks or any animals.
Patients should be encouraged to alert all new health care professionals, including dentists, about their asplenic or hyposplenic status.
Patient medical records should prominently display that the patient has had a splenectomy or is functionally hyposplenic.

Immunoprophylaxis
Pneumococcal, meningococcal, and Haemophilus influenzae type B vaccinations should be given at least 14 days before splenectomy or as soon as possible postsurgery; booster injections every 5 to 6 years should be considered in the case of pneumococcal vaccine. (Note: the measurement of antibody levels may serve as a guide to the need for revaccination, but such testing is not widely available and interpretation may be difficult.)
Annual influenza immunization is advisable.
Ongoing documentation and communication of immunization status is necessary.
Immunization should never produce a false sense of complacency in patients or physicians.

Chemoprophylaxis
Failures of drug prophylaxis have been reported, as have infections caused by penicillin-resistant strains of pneumococcus.
Traditional prophylaxis with orally administered penicillin has been replaced by drugs such as amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, or cefuroxime.
Lifelong prophylaxis may be considered in the case of immunocompromised patients, but there exists no consensus among experts about this management strategy.
If a decision is made to provide standby antibiotics, patients should have a supply of antipneumococcal antibiotics available to take if febrile illness develops, especially if immediate medical attention is not available.
Patients developing infection despite prophylactic measures (eg, administration of antibiotics, vaccination) should be given systemic antibiotics (eg, ceftriaxone, cefotaxime) and promptly admitted to a hospital.


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Infectious Emergencies in Critically Ill Patients

Patient 1 is admitted to the ICU and empiric administration of vancomycin and ceftriaxone, as well as aggressive intravenous hydration, is provided while workup for suspected OPSI is in progress. Results of sputum, urine, blood, stool, and cerebrospinal fluid cultures come back negative for any organisms. The patient improves clinically within 24 hours and is transferred out of the ICU. The next day he is discharged from the hospital without further antibiotic management. When the patient comes for a follow-up examination in the outpatient clinic, his recent febrile episode is attributed to viral gastroenteritis.
NECROTIZING FASCIITIS

CASE 2 PRESENTATION

A previously healthy 56-year-old man presents to the ED because of left lower extremity pain. He reports bumping his calf on a coffee table early last week but says he did not notice any local injury until 2 days ago when he detected redness and warmth at the site. On examination, he appears toxic and uncomfortable because of the pain. Vital signs include a temperature of 38.9°C (102°F), a blood pressure of 70/50 mm Hg, a heart rate of 135 bpm, and a respiratory rate of 24 breaths/min. The leg is diffusely swollen and erythematous and feels wooden below the knee. A few bullae are present. No abrasion is detected at the trauma site.

- What is the most appropriate treatment of this patient’s condition?

REVIEW OF NECROTIZING FASCIITIS

General Considerations

Severe skin and soft-tissue infections such as NF (Figure 1) differ from milder, superficial infections in their clinical presentation, coexisting systemic manifestations, and treatment strategies. These infections are deep, involving fascial and/or muscle compartments, and potentially devastating, capable of causing major tissue destruction and a fatal outcome. Five clinical features suggest the presence of a deep and severe infection of the skin and deeper structures: (1) severe pain; (2) bullous lesions; (3) gas in the soft tissues; (4) systemic toxicity manifested by fever, leukocytosis, delirium, and renal failure; and (5) rapid spread centrally along fascial planes.

NF is a relatively rare infection involving subcutaneous tissues with extensive undermining and tracking along fascial planes. Extension from a skin lesion is evident in 80% of cases. The initial lesion is often trivial, such as a minor abrasion, an insect bite, an injection site, or a boil. NF caused by group A streptococci has been acquired via skin lesions of varicella in children.

Epidemiology

The mortality rate in cases of NF is approximately 20% to 30%. Morbidity and mortality are adversely influenced by delay in diagnosis and by increased age. Mortality also is higher in cases associated with toxic shock syndrome, diabetes mellitus, advanced arteriosclerotic vascular disease, and skin or soft-tissue lesions that progress into the buttocks or back muscles or onto the chest wall.

Etiology and Pathogenesis

The most common cause of NF is severe streptococcal infection. NF caused by group A streptococci, previously known as streptococcal gangrene, is commonly associated with early onset of shock and organ failure—characteristics that are used to define streptococcal toxic shock syndrome. Several reports indicate that the incidence of severe streptococcal infections increased in the 1990s. Strains of group A streptococci isolated from patients with invasive disease have been predominantly M types 1, 3, and 12, which produce pyrogenic exotoxin A or B (or both). Bisno and Stevens have
postulated that the apparent increased aggressiveness of group A streptococci may result from a change in their virulence factors, including production of streptococcal pyrogenic toxins A or B. The streptococcal pyrogenic exotoxins belong to the group of superantigens, which have the capacity to superstimulate the immune system and thereby induce a cascade of cytokines, assumed to be responsible for the induction of toxic shock syndrome. Other authors have found that toxin production does not correlate with mortality and have postulated that absence of immunity against group A streptococci M protein or its toxins is responsible for the regional occurrence of clusters of serious group A streptococcal infections.

NF occurs in monomicrobial or polymicrobial forms. Monomicrobial forms are caused by group A streptococci, S. aureus, or anaerobic streptococci. Staphylococci and β-hemolytic streptococci occur with about equal frequency, and approximately one third of affected patients will have both concurrently. The majority of these infections manifest themselves in the extremities; approximately two thirds occur in a lower extremity. There is often an underlying cause, such as diabetes mellitus, arteriosclerotic vascular disease, or venous insufficiency with edema. In some instances, a chronic vascular ulcer evolves into a more acute process. Mortality in patients with NF are typically disoriented and lethargic. They there is systemic toxicity causing high fevers. Patients with NF are typically disoriented and lethargic. They generally first report nonspecific symptoms such as pain and fever. The presence of marked systemic toxicity and severe pain out of proportion to local findings should suggest the possibility of NF. Although most often acute, NF may follow a subacute progressive course.

The initial clinical manifestation of NF is a slowly advancing cellulitis. Over the next 2 to 4 days, however, there is systemic toxicity causing high fevers. Patients with NF are typically disoriented and lethargic. They generally first report nonspecific symptoms such as pain and fever. The presence of marked systemic toxicity and severe pain out of proportion to local findings should suggest the possibility of NF. Although most often acute, NF may follow a subacute progressive course. The local site where NF is first detected typically has the following characteristics: cellulitis (90%), edema (80%), and skin discoloration or gangrene (70%); anesthesia of the involved skin also frequently occurs. Whereas, overlying cellulitis is often present and is usually easily recognizable, involvement of the deeper fascial planes is suggested by the following 3 features: (1) failure of the patient to respond to initial antibiotic therapy; (2) the hard, wooden feel of the subcutaneous tissue; and (3) systemic toxicity, often with altered mental status.

The affected area is initially red, hot, shiny, swollen (without sharp margins), and exquisitely tender. The process progresses over several days, with the involved skin displaying the characteristic blue-gray, ill-defined patches as early as 36 hours after onset. Within 3 to 5 days, cutaneous bullae and necrosis occur. By this time, the involved area is no longer tender, having become anesthetic because of thrombosis of small blood vessels and destruction of superficial nerves. The sine qua non of NF is the presence of fascial necrosis with widespread undermining of the skin. The involved fascia and subcutaneous fat are edematous, dull gray in color, and necrotic, with serosanguineous exudate. Underlying muscle or bone can become involved.

Clinical and Laboratory Findings

On physical examination, patients with NF generally appear toxic and have tachycardia, tachypnea, and hypotension. Local edema and erythema are often present. The most distinguishing clinical finding is the wooden-hard feel of the subcutaneous tissues. In many
cases, clinicians can observe a broad erythematous tract in the skin along the route of the fascial plane as the infection advances cephalad in an extremity. If there is an open wound, probing the edges with a blunt instrument permits ready dissection of the superficial fascial planes, well beyond the wound margins.7 Subcutaneous emphysema or crepitus may occur and can be detected on radiographs. Gas in the soft tissues is usually evident radiographically when NF is caused by mixed organisms but not as commonly when it is caused by group A streptococci.8 A computed tomography scan or magnetic resonance image may show exudate extending along the fascial plane. The most significant diagnostic feature of necrotizing fasciitis is the appearance of the fascial planes at surgery. On direct inspection, the fascia is swollen and dull gray, with stringy areas of necrosis and a thin brownish exudate emerging from the wound. Even on deep dissection, however, there is no true pus. Extensive undermining of surrounding tissues is present, and the fascial planes can be dissected with a gloved finger or blunt instrument.

Results of Gram stain of the exudate reveal the presence of pathogens and provide an early clue to therapy. Culture material is best obtained from the deep tissues. A definitive bacteriologic diagnosis can be established only by culture of the fascia at operation or by positive blood culture results.7 Other abnormal laboratory findings in patients with NF include leukocytosis, thrombocytopenia, disseminated intravascular coagulopathy, a low serum albumin level, and an increased serum creatine kinase level. Anemia, hypocalcemia, and hypotension also are frequently present.

Management

Surgical intervention is one of the most important therapeutic modalities in cases of necrotizing fasciitis. The decision to undertake aggressive surgery should be based on the following 3 criteria: (1) failure to respond to antibiotic therapy after a reasonable trial; (2) profound toxicity, fever, hypotension, or advancement of the skin and soft-tissue infection during antibiotic therapy; and (3) extensive necrosis of the local wound with easy dissection along the fascia, indicating the need for more complete débridement.7 Incisions should be performed to the deep fascia, and all necrotic skin and nonviable fascia should be débrided. Because the first procedure is almost never sufficient to determine the extent of involvement, additional incision and débridement are almost always necessary. Aggressive fluid and electrolyte replacement is vital. Antimicrobial therapy can minimize the extent of necessary surgical interven-

tion. Therapy must be directed at the isolated pathogens and used for a prolonged period, usually for 2 to 3 weeks.

Hyperbaric oxygen may or may not be beneficial for patients with NF; anecdotal reports have provided contradictory information.13 Intravenous administration of immune globulin, which contains considerable amounts of toxin-neutralizing antibodies, has been recommend-
ed for invasive group A streptococcal infection on the assumption that the antibodies will bind streptococcal exotoxins, although reports of the efficacy of this strategy are not conclusive.12 Clindamycin should be considered for patients with established invasive group A streptococcal infection, because this drug abruptly stops the metabolic activity of the streptococci and thus halts further production of exotoxins.12 In addition to clindamycin being a potent suppressor of bacterial toxin synthesis, the drug’s efficacy may be related to its multifactorial ability to modulate the immune response and its greater activity versus the β-lactams in the stationary phase of bacterial growth.9 Interestingly, retrospective studies suggest that nonsteroidal anti-inflammatory agents may be associated with the development of NF, perhaps via inhibition of granulocytic function, so these agents should be avoided in patients with any soft-tissue infection.13

FOLLOW-UP DISCUSSION OF PATIENT 2

The patient was admitted to the ICU, where aggressive volume resuscitation and broad spectrum antibiotics are started. Disease progression in the lower extremity continues in patient 2 despite intravenous administration of piperacillin/tazobactam and clindamycin. The next day, he undergoes operative débridement; fascial necrosis and myonecrosis are detected. After blood and operative specimens grow penicillin-sensitive group A β-hemolytic streptococci, the piperacillin/tazobactam is replaced by penicillin, and immunoglobulin is administered intravenously. Recurrent débridement and intensive care management are required over the next week until early clinical signs of improvement are noted.

SEPSIS

CASE 3 PRESENTATION

A 59-year-old man with a history of hypertension and benign prostatic hypertrophy comes to the ED with fever (temperature to 38.9°C [102°F]) and urinary frequency. He underwent biopsy of a prostatic nodule yesterday. He is diaphoretic, with a respiratory rate of
30 breaths/min. Systolic blood pressure is 90 mm Hg. Oxygen saturation by pulse oximetry is 89%. Chest radiographs reveal no abnormalities. Electrocardiography reveals sinus tachycardia. Leukocyte count is $12 \times 10^3$/mm$^3$ with a left shift. Urinalysis shows 50 leukocytes per high-power field.

- What is the differential diagnosis of the patient’s hypotension?

**THE SEPSIS SYNDROME**

**Definitions, Epidemiology, and Etiology**

The systemic response to infection has been termed sepsis (Figure 2). In recent decades the reported incidence of sepsis has increased dramatically, largely due to an increased number of invasive procedures being performed, immunosuppressive therapy, and the advancing age of the population. Sepsis develops in 750,000 people annually, and more than 210,000 of them die. Approximately one third to one half of patients who develop sepsis have culture-positive blood. Studies from the past 2 decades show an increase in the number of cases involving gram-positive organisms, compared with earlier studies suggesting that over half of the cases were caused by gram-negative bacteria. The toxic shock toxins of *S. aureus* and *Streptococcus pyogenes* can produce septic shock even when blood cultures are negative for the organisms. Overall, an increased number of fungal, viral, mycobacterial, and parasitic causes of sepsis has been reported, most likely owing to the increased number of immunocompromised patients.

The related term systemic inflammatory response syndrome (SIRS) describes the inflammatory process that can arise in response to and even sometimes in the absence of an infectious invader. Thus, when SIRS is caused by an infection, the terms SIRS and sepsis are synonymous. Specific clinical syndromes describe the progressive increase in the systemic inflammatory response to infection. Besides an initial SIRS, 3 hierarchical stages associated with infection have been defined—sepsis, severe sepsis, and septic shock (Table 2). Severe sepsis denotes a more advanced degree of organ compromise; progressive increases in the number of positive blood cultures, end-organ failure, and mortality are seen with each hierarchical stage of sepsis. Septic shock, a subset of severe sepsis, is defined as sepsis-induced hypotension that persists despite adequate fluid resuscitation and is characterized by the presence of hypoperfusion abnormalities or organ dysfunction.

Noninfectious causes of SIRS include pancreatitis, visceral ischemia, multiple trauma and tissue injury, hemorrhagic shock, immune-mediated organ injury, and exogenous administration of mediators of the inflammatory process (eg, tumor necrosis factor [TNF], other cytokines). A frequent complication of SIRS is the development of organ system dysfunction in conditions such as acute lung injury, shock, renal failure, and multiple organ dysfunction syndrome.

**General Clinical Manifestations**

Even before they have elevated temperatures or onset of chills, patients with bacteremia may begin to hyperventilate. Thus, the earliest metabolic change in patients with sepsis syndrome is often a resultant respiratory alkalosis. Change in mental status also can be a telling clue. The clinician should likewise be acutely aware that the clinical findings of hypotension, decreased urine output and/or circulating platelet level, and evidence of bleeding—even in the absence of fever and chills—could be manifestations of a systemic infectious process or of systemic absorption of microbial toxins from a focal infectious process.

Decreases in patients’ leukocyte count occur early in
response to bacteremia, owing to redistribution of neutrophils from the circulating to the marginated pool, as platelet-activating factor and cytokines induce adhesion molecules specific for neutrophils. The coagulation system is further activated, and platelet adherence is manifested by a decreasing circulating platelet count.

Cutaneous manifestations also may be seen in patients with sepsis and may provide a clue to the infectious etiology. For example, erythroderma resulting from the pathophysiologic action of pyrogenic or erythrogenic toxins of gram-positive organisms may be striking. Similarly, ecthyma-type lesions are strongly suggestive of infection with *Pseudomonas aeruginosa*. The clinical manifestations of disseminated intravascular coagulopathy vary—from none, to scattered petechiae of the skin and mucous membranes, to thrombotic occlusion of end arteries with ischemic necrosis of the distal fingers and toes.

Many patients with sepsis have transient hypotension or oliguria that is quickly ameliorated by prompt corrective measures (eg, aggressive fluid administration). Others progress from an initial phase of hypotension, tachycardia, and peripheral vasodilation (previously known as “warm shock”) to a moribund phase of deep pallor, intense vasoconstriction, and anuria (previously known as “cold shock”). The latter state clearly reflects the inability of compensatory mechanisms to maintain perfusion, even to vital organs.

Many patients with sepsis have bacteremia originating from the lungs. In addition, diffuse pneumonitis can develop secondary to bacteremia; this condition, when of overwhelming severity, is referred to as acute respiratory distress syndrome. Characteristic findings include hypoxia, evidence of a right-to-left shunt, and diffuse pulmonary infiltrates in the presence of a normal pulmonary wedge pressure, indicating noncardiogenic pulmonary edema.

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**Table 2. Standard Definitions for Sepsis and Organ Failure**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Presence of viable bacteria in the blood</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome</td>
<td>The systemic inflammatory response to a wide variety of severe clinical insults, manifested by 2 or more of the following conditions: (1) temperature &gt; 38°C (100.4°F) or &lt; 36°C (96.8°F); (2) heart rate &gt; 90 bpm; (3) respiratory rate &gt; 20 breaths/min, or PaCO₂ &lt; 32 mm Hg; and (4) leukocyte count &gt; 12 × 10³/mm³, or &lt; 4 × 10³/mm³, or containing &gt; 10% immature band forms</td>
</tr>
<tr>
<td>Sepsis</td>
<td>The systemic inflammatory response to infection. When associated with infection, manifestations of sepsis are the same as those previously defined for systemic inflammatory response syndrome; it should be determined whether they are a part of the direct systemic response to the presence of an infectious process and represent an acute alteration from baseline in the absence of other known causes for such abnormalities.</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>Sepsis 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.</td>
</tr>
<tr>
<td>Septic shock</td>
<td>A subset of severe sepsis defined as sepsis-induced hypotension despite adequate fluid resuscitation along with the 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, but they would still be considered to have septic shock.</td>
</tr>
<tr>
<td>Multiple organ dysfunction syndrome</td>
<td>Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention</td>
</tr>
<tr>
<td>Sepsis-induced hypotension</td>
<td>A systolic blood pressure &lt; 90 mm Hg or a reduction in blood pressure of at least 40 mm Hg from baseline in the absence of other causes for hypotension</td>
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</table>

Organ Failure and Septic Shock

Exactly how a critically ill patient with sepsis develops multiple system organ failure (MSOF) is still a mystery. It is interesting, however, that the progressive dysfunction of systems may occur in a predictable manner. During the first 72 hours of the original insult, respiratory failure commonly occurs. This is followed by hepatic failure (5–7 days), gastrointestinal bleeding (10–15 days) and finally renal failure (11–17 days), in the typical case. In addition, the extent to which an individual organ is likely to be damaged in patients with MSOF is variable. Organ failure in cases of sepsis is largely the result of advances in medical support systems that have improved the ability to sustain life, even after severe insults.

As sepsis progresses in a critically ill patient, there are changes in the sympathetic tone, giving rise to tachycardia and associated hypotension. By reflex, there is an increase in respiratory drive, and patients experience tachypnea and hyperpnea. Hypoperfusion of the liver and periphery lead to profound lactic acidosis. Although mental status changes such as agitation may be caused by increased levels of catecholamines, stupor and coma are more likely to result from hypoperfusion of the central nervous system. An increased sympathetic tone causes the release of acetylcholine, which stimulates diaphoresis.

When patients with sepsis are monitored physiologically, an increased cardiac output is evident as systemic vascular resistance decreases. However, with low perfusion, myocardial depression occurs and cardiac output decreases. Thus, organ failure is best viewed as cell death resulting from tissue hypoperfusion. The 3 factors determining global blood flow are cardiac pump function, blood volume, and peripheral vasomotor tone. In cases of sepsis, vasomotor tone decreases and capillaries leak; damage to the capillary endothelium is induced by neutrophil lysosomal enzymes and reactive oxygen molecules, causing subsequent leakage of vascular contents. Myocardial depression and altered vascular tone appear to be interrelated in cases of septic shock and characterize its fatal course.

Molecular Events and Intervention Studies

Molecular Events

Sepsis is viewed physiologically as a proinflammatory and procoagulant response to invading pathogens. The development of SIRS and multiple organ dysfunction syndrome is linked to host-derived expression of cytokines. Inflammation can be considered a cytokine-regulated process that is both essential for normal host defense and detrimental to bodily function. Elevated levels of TNF-α and interleukin 6 (IL-6) are commonly seen in the blood of patients with sepsis, with absolute levels being crucially predictive of mortality; the persistence of elevated levels is highly predictive of the development of multiple organ dysfunction syndrome and/or death. Bacterial endotoxins initiate sepsis associated with infection with gram-negative rod bacteria.

The lipid A portion of lipopolysaccharide (LPS) is especially important in stimulating phagocytes, endothelial cells, and other cells to release mediators (eg, IL-1, TNF) that amplify LPS-dependent host responses. LPS first interacts with LPS-binding protein, which transfers LPS to CD14, a receptor on macrophages and B cells. The consequence of LPS binding to the LPS-recognition complex (of which CD14 is a component) is cell activation, which leads to new gene expression. Intracellular kinase cascades have been shown to play a vital role in LPS signaling. The lipid-containing cell-wall material from gram-positive organisms (ie, lipo-teichoic acid [LTA]) elicits a similar inflammatory response but is less potent. It is now known that LPS and LTA elicit a similar intracellular cascade of cytokine production by binding Toll-like receptors (TLR-4 for LPS; TLR-2 for LTA; other TLRs for fungi, viruses, and so on). TLRs may function as receptors of the innate immune system. This fact might explain the long-known clinical observation that non-LPS-associated infections often result in sepsis.

The sepsis biochemical cascade is complex, with redundancies built into an incompletely understood series of pathways. Endogenous mediators include cytokines (IL-1α, IL-1β, IL-1 receptor antagonist, IL-2, IL-6, IL-8, IL-10, TNF-α, interferon γ), oxygen free radicals, nitric oxide (a major mediator of vascular smooth muscle tone), arachidonic acid metabolites, platelet-activating factor, and myocardial depressant substance. The major clinical manifestations result from mediator activity in the hypothalamus, the capillary endothelium, and vascular smooth-muscle cells. Effects of cytokines are pleiotropic and sometimes paradoxical. The identification of TNF-α as an important mediator of septic shock suggests that the sepsis syndrome is an example of immune system overresponsiveness to invading pathogens. However, a shift has occurred in the way investigators view sepsis. Rather than the prevailing theory that sepsis represents an uncontrolled inflammatory response, evidence indicates that the immune system becomes severely compromised and unable to eradicate pathogens. Patients with sepsis have features consistent with immunosuppression. Although initially inflammatory mediators are increased, as sepsis persists, there is a shift toward antiinflammatory (Th2) cytokines. Apoptotic cell death may trigger sepsis-induced anergy.
Intervention Studies

Nearly 70 clinical trials of various therapies for sepsis have been performed, with generally disappointing results. Not surprisingly, single therapies targeting unique inflammatory pathways can easily fail. The cytokines released in sepsis are rapidly deployed and hit their cellular targets quickly. Thus, immunotherapies will have to be initiated early or perhaps administrated prophylactically to be effective. So far, no compelling data exist to support immunotherapy with IL-1 receptor antagonist, monoclonal antibody to TNF, TNF receptors, or antiendotoxin monoclonal antibodies.

There are several synergistic pathways by which inflammatory and procoagulant mechanisms can initiate and perpetuate organ injury in patients with sepsis. Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation, modulating coagulation and inflammation associated with severe sepsis. The conversion of protein C to activated protein C may be impaired during sepsis, as a result of the down-regulation of thrombomodulin by inflammatory cytokines. Reduced levels of protein C are found in the majority of patients with sepsis and are associated with an increased risk for death. Activated protein C therapy has recently been approved by the US Food and Drug Administration (see Management of Sepsis). Other trials of agents designed to inhibit coagulation and inflammation have revealed conflicting results and some are underway.

MANAGEMENT OF SEPSIS

Four elements of therapy for sepsis syndrome and septic shock have been widely accepted by clinicians: (1) correction of the pathologic condition that allowed the bacteria to enter the bloodstream, (2) optimization of intravascular volume, (3) administration of empiric antimicrobial therapy appropriate for bacteria commonly encountered at the presumed portal of entry, and (4) administration of vasoactive drugs.

Underestimating the amount of fluid that needs to be replaced is a serious error in the management of septic shock. Fluid requirements for the initial resuscitation of patients with septic shock are frequently large, with up to 10 L of crystalloid or 4 L of colloid being required in the first 24 hours. If fluid replacement alone fails to correct blood pressure, despite a normal or elevated cardiac output, then administration of a vasopressor such as dopamine or norepinephrine is indicated. Vasopressors increase cardiac contractility and improve vasomotor tone; failure of these sympathomimetic agents to have their desired effects in the presence of an adequate preload might be associated with conditions such as acidosis (ie, pH < 7.3), hypocalcemia, adrenal insufficiency, or hypoglycemia. Optimization of hemodynamic parameters should take place early in management, and may lead to an improved outcome if adjustment of cardiac preload, afterload, and contractility to balance oxygen delivery with demand is accomplished within the first 6 hours.

The treatment of sepsis has advanced significantly over the past few years. Most notably, activated protein C, an anti-inflammatory and anticoagulant agent, has been shown to be effective in reducing mortality in patients with severe sepsis. A randomized, double-blind study of 1690 patients demonstrated that drotrecogin alfa (activated), a recombinant formulation of activated protein C, significantly reduced mortality (absolute reduction in 28-day mortality rate of 6.1%) in patients with severe sepsis. This study excluded patients at higher risk for bleeding. Hemorrhage is a major risk associated with the administration of activated protein C. Several mechanisms may account for the combined anticoagulant and anti-inflammatory effects of this drug, including reduction of plasma D-dimer levels and serum levels of IL-6, as well as reduction of TNF-α production by monocytes.

On the basis of these trial results, activated protein C is now recommended for patients who meet the inclusion criteria, including evidence of end-organ dysfunction with shock, acidosis, oliguria, or hypoxemia. Drotrecogin alfa (activated) was approved in 2001 for the treatment of severe sepsis in certain seriously ill patients with a high risk of death. The drug is specifically indicated for reducing mortality in patients with sepsis associated with organ failure who have a high risk of death as determined by APACHE II (the Acute Physiology and Chronic Health Evaluation) score.

Other therapies have recently been shown to be of value in the treatment of sepsis. Tight control of blood glucose levels (intensive insulin therapy to maintain blood glucose at a level between 80 and 110 mg/dL) has been shown to improve mortality in patients with multi-organ failure and sepsis, regardless of whether patients have a history of diabetes. Although administration of high doses of corticosteroids has not been shown to be beneficial in the treatment of sepsis, low doses reduced the risk of death in patients with septic shock and relative adrenal insufficiency in a study reported by Annane and colleagues.

FOLLOW-UP DISCUSSION OF PATIENT 3

After receiving supplemental oxygen, empiric antibiotic therapy with ampicillin-sulbactam and gentamicin, patient 3 is admitted to the ICU. Urine output is decreased. A bolus of normal saline, administered
intravenously, does not increase blood pressure. Administration of dopamine results in improved systolic blood pressure. Urine culture grows more than 10^5 colonies of *Proteus mirabilis* sensitive to all antibiotics tested. Prostatic ultrasonography reveals a parenchymal abscess, which is surgically drained. Antibiotics are narrowed to cefazolin, administered intravenously, and the patient’s condition improves. Because invasive measures are no longer required, management is continued on the general medical ward.

**REFERENCES**