proteinuria. Leukopenia may develop. The neutrophils may contain toxic granulations, Döhle bodies, or cytoplasmic vacuoles. As the septic response becomes more severe, thrombocytopenia worsens (often with prolonged thrombin time, decreased fibrinogen, and the presence of D-dimers, suggesting DIC), azotemia and hyperbilirubinemia become more prominent, and levels of aminotransferases rise. Active hemolysis suggests clostridial bacteremia, malaria, a drug reaction, or DIC; in the case of DIC, microangiopathic changes may be seen on a blood smear.

During early sepsis, hyperventilation induces respiratory alkalosis. With respiratory muscle fatigue and the accumulation of lactate, metabolic acidosis (with increased anion gap) typically supervenes. Evaluation of arterial blood gases reveals hypoxemia that is initially correctable with supplemental oxygen but whose later refractoriness to 100% oxygen inhalation indicates right-to-left shunting. The chest radiograph may be normal or may show evidence of underlying pneumonia, volume overload, or the diffuse infiltrates of ARDS. The electrocardiogram may show only sinus tachycardia or nonspecific ST–T wave abnormalities.

Most diabetic patients with sepsis develop hyperglycemia. Severe infection may precipitate diabetic ketoacidosis that may exacerbate hypotension (Chap. 417). Hypoglycemia occurs rarely and may indicate adrenal insufficiency. The serum albumin level declines as sepsis continues. Hypocalcemia is rare.

DIAGNOSIS

There is no specific diagnostic test for sepsis. Diagnostically sensitive findings in a patient with suspected or proven infection include fever or hypothermia, tachypnea, tachycardia, and leukocytosis or leukopenia (Table 325-1); acutely altered mental status, thrombocytopenia, an elevated blood lactate level, respiratory alkalosis, or hypotension also should suggest the diagnosis. The systemic response can be quite variable, however. In one study, 36% of patients with severe sepsis had a normal temperature, 40% had a normal respiratory rate, 10% had a normal pulse rate, and 33% had normal white blood cell counts. Moreover, the systemic responses of uninfected patients with other conditions may be similar to those characteristic of sepsis. Examples include pancreatitis, burns, trauma, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, postcardiopulmonary bypass syndrome, anaphylaxis, tumor-associated lactic acidosis, and drug overdose.

Definitive etiologic diagnosis requires identification of the causative microorganism from blood or a local site of infection. At least two blood samples should be obtained (from two different venipuncture sites) for culture; in a patient with an indwelling catheter, one sample should be collected from each lumen of the catheter and another via venipuncture. In many cases, blood cultures are negative; this result can reflect prior antibiotic administration, the presence of slow-growing or fastidious organisms, or the absence of microbial invasion of the bloodstream. In these cases, Gram's staining and culture of material from the primary site of infection or from infected cutaneous lesions may help establish the microbial etiology. Identification of microbial DNA in peripheral blood or tissue samples by polymerase chain reaction may also be definitive. The skin and mucosae should be examined carefully and repeatedly for lesions that might yield diagnostic information. With overwhelming bacteremia (e.g., pneumococcal sepsis in splenectomized individuals; fulminant meningococcemia; or infection with *V. vulnificus*, *B. pseudomallei*, or *Y. pestis*), microorganisms are sometimes visible on buffy coat smears of peripheral blood.

TREATMENT SEVERE SEPSIS AND SEPTIC SHOCK

Patients in whom sepsis is suspected must be managed expeditiously. This task is best accomplished by personnel who are experienced in the care of the critically ill. Successful management requires urgent measures to treat the infection, to provide hemodynamic and respiratory support, and to remove or drain infected tissues. These measures should be initiated within 1 h of the patient's presentation with severe sepsis or septic shock. Rapid assessment and diagnosis are therefore essential.

ANTIMICROBIAL AGENTS

Antimicrobial chemotherapy should be started as soon as samples of blood and other relevant sites have been obtained for culture. A large retrospective review of patients who developed septic shock found that the interval between the onset of hypotension and the administration of appropriate antimicrobial chemotherapy was the major determinant of outcome; a delay of as little as 1 h was associated with lower survival rates. Use of "inappropriate" antibiotics, defined on the basis of local microbial susceptibilities and published guidelines for empirical therapy (see below), was associated with fivefold lower survival rates, even among patients with negative cultures.

It is therefore very important to promptly initiate empirical antimicrobial therapy that is effective against both gram-positive and gram-negative bacteria (Table 325-3). Maximal recommended doses of antimicrobial drugs should be given intravenously, with adjustment for impaired renal function when necessary. Available information about patterns of antimicrobial susceptibility among bacterial isolates from the community, the hospital, and the patient should be taken into account. When culture results become available, the regimen can often be simplified because a single antimicrobial agent is usually adequate for the treatment of a known pathogen. Meta-analyses have concluded that, with one exception, combination antimicrobial therapy is not superior to monotherapy for treating gram-negative bacteremia; the exception is that aminoglycoside monotherapy for *P. aeruginosa* bacteremia is less effective than the combination of an aminoglycoside with an antipseudomonal β-lactam agent. Empirical antifungal therapy should be strongly considered if the septic patient is already receiving broad-spectrum antibiotics or parenteral nutrition, has been neutropenic for ≥5 days, has had a long-term central venous catheter in place, or has been hospitalized in an ICU for a prolonged period. The chosen antimicrobial regimen should be reconsidered daily in order to provide maximal efficacy with minimal resistance, toxicity, and cost.

Most patients require antimicrobial therapy for at least 1 week. The duration of treatment is typically influenced by factors such as the site of tissue infection, the adequacy of surgical drainage, the patient's underlying disease, and the antimicrobial susceptibility of the microbial isolate(s). The absence of an identified microbial pathogen is not necessarily an indication for discontinuing antimicrobial therapy because "appropriate" antimicrobial regimens seem to be beneficial in both culture-negative and culture-positive cases.

REMOVAL OF THE SOURCE OF INFECTION

Removal or drainage of a focal source of infection is essential. In one series, a focus of ongoing infection was found in ~80% of surgical ICU patients who died of severe sepsis or septic shock. Sites of occult infection should be sought carefully, particularly in the lungs, abdomen, and urinary tract. Indwelling IV or arterial catheters should be removed and the tip rolled over a blood agar plate for quantitative culture; after antibiotic therapy has been initiated, a new catheter should be inserted at a different site. Foley and drainage catheters should be replaced. The possibility of paranasal sinusitis (often caused by gram-negative bacteria) should be considered if the patient has undergone nasal intubation or has an indwelling nasogastric or feeding tube. Even in patients without abnormalities on chest radiographs, computed tomography (CT) of the chest may identify unsuspected parenchymal, mediastinal, or pleural disease. In the neutropenic patient, cutaneous sites of tenderness and erythema, particularly in the perianal region, must be carefully sought. In patients with sacral or ischial decubitus ulcers, it is important to exclude pelvic or other soft tissue pus collections with CT or magnetic resonance imaging (MRI). In patients with severe sepsis arising from the urinary tract, sonography or CT should be used to rule out ureteral obstruction, perinephric abscess, and renal abscess. Sonographic or CT imaging of the upper abdomen may disclose