Histopathologic examination shows bacteria in and around the wall of a small vessel, with little or no neutrophilic response. Hemorrhagic or bullous lesions in a septic patient who has recently eaten raw oysters suggest *V. vulnificus* bacteremia, whereas such lesions in a patient who has recently sustained a dog bite may indicate bloodstream infection due to *Capnocytophaga canimorsus* or *Capnocytophaga cynodegmi*. Generalized erythroderma in a septic patient suggests the toxic shock syndrome due to *S. aureus* or *S. pyogenes*.

Gastrointestinal manifestations such as nausea, vomiting, diarrhea, and ileus may suggest acute gastroenteritis. Stress ulceration can lead to upper gastrointestinal bleeding. Cholestatic jaundice, with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase, may precede other signs of sepsis. Hepatocellular or canalicular dysfunction appears to underlie most cases, and the results of hepatic function tests return to normal with resolution of the infection. Prolonged or severe hypotension may induce acute hepatic injury or ischemic bowel necrosis.

Many tissues may be unable to extract oxygen normally from the blood, so that anaerobic metabolism occurs despite near-normal mixed venous oxygen saturation. Blood lactate levels rise early because of increased glycolysis as well as impaired clearance of the resulting lactate and pyruvate by the liver and kidneys. The blood glucose concentration often increases, particularly in patients with diabetes, although impaired gluconeogenesis and excessive insulin release on occasion produce hypoglycemia. The cytokine-driven acute-phase response inhibits the synthesis of transthyretin while enhancing the production of C-reactive protein, fibrinogen, and complement components. Protein catabolism is often markedly accelerated. Serum albumin levels decline as a result of decreased hepatic synthesis and the movement of albumin into interstitial spaces.

MAJOR COMPLICATIONS

Cardiopulmonary Complications Ventilation-perfusion mismatching produces a fall in arterial Po_2 early in the course. Increasing alveolar epithelial injury and capillary permeability result in increased pulmonary water content, which decreases pulmonary compliance and interferes with oxygen exchange. In the absence of pneumonia or heart failure, progressive diffuse pulmonary infiltrates and arterial hypoxemia occurring within 1 week of a known insult indicate the development of mild acute respiratory distress syndrome (ARDS) (200 mmHg < Pao_2/Fio_2 ≤ 300 mmHg), moderate ARDS (100 mmHg < Pao_2/Fio_2 ≤ 200 mmHg), or severe ARDS (Pao_2/Fio_2 ≤100 mmHg). Acute lung injury or ARDS develops in ~50% of patients with severe sepsis or septic shock. Respiratory muscle fatigue can exacerbate hypoxemia and hypercapnia. An elevated pulmonary capillary wedge pressure (>18 mmHg) suggests fluid volume overload or cardiac failure rather than ARDS. Pneumonia caused by viruses or by *Pneumocystis* may be clinically indistinguishable from ARDS.

Sepsis-induced hypotension (see "Septic Shock," above) usually results initially from a generalized maldistribution of blood flow and blood volume and from hypovolemia that is due, at least in part, to diffuse capillary leakage of intravascular fluid. Other factors that may decrease effective intravascular volume include dehydration from antecedent disease or insensible fluid losses, vomiting or diarrhea, and polyuria. During early septic shock, systemic vascular resistance is usually elevated and cardiac output may be low. After fluid repletion, in contrast, cardiac output typically increases and systemic vascular resistance falls. Indeed, normal or increased cardiac output and decreased systemic vascular resistance distinguish septic shock from cardiogenic, extracardiac obstructive, and hypovolemic shock; other processes that can produce this combination include anaphylaxis, beriberi, cirrhosis, and overdoses of nitroprusside or narcotics.

Depression of myocardial function, manifested as increased end-diastolic and systolic ventricular volumes with a decreased ejection fraction, develops within 24 h in most patients with severe sepsis. Cardiac output is maintained despite the low ejection fraction because ventricular dilation permits a normal stroke volume. In survivors, myocardial function returns to normal over several days. Although myocardial dysfunction may contribute to hypotension, refractory hypotension is usually due to low systemic vascular resistance, and death most often results from refractory shock or the failure of multiple organs rather than from cardiac dysfunction per se.

Adrenal Insufficiency The diagnosis of adrenal insufficiency may be very difficult in critically ill patients. Whereas a plasma cortisol level of ≤15 μg/mL (≤10 μg/mL if the serum albumin concentration is <2.5 mg/dL) indicates adrenal insufficiency (inadequate production of cortisol), many experts now feel that the adrenocorticotropic hormone (CoSyntropin®) stimulation test is not useful for detecting less profound degrees of corticosteroid deficiency in patients who are critically ill. The concept of critical illness–related corticosteroid insufficiency (CIRCI) was proposed to encompass the different mechanisms that may produce corticosteroid activity that is inadequate for the severity of a patient's illness. Although CIRCI may result from structural damage to the adrenal gland, it is more commonly due to reversible dysfunction of the hypothalamic-pituitary axis or to tissue corticosteroid resistance resulting from abnormalities of the glucocorticoid receptor or increased conversion of cortisol to cortisone. The major clinical manifestation of CIRCI is hypotension that is refractory to fluid replacement and requires pressor therapy. Some classic features of adrenal insufficiency, such as hyponatremia and hyperkalemia, are usually absent; others, such as eosinophilia and modest hypoglycemia, may sometimes be found. Specific etiologies include fulminant *N. meningitidis* bacteremia, disseminated tuberculosis, AIDS (with cytomegalovirus, *Mycobacterium avium-intracellulare*, or *Histoplasma capsulatum* disease), or the prior use of drugs that diminish glucocorticoid production, such as glucocorticoids, megestrol, etomidate, or ketoconazole.

Renal Complications Oliguria, azotemia, proteinuria, and nonspecific urinary casts are frequently found. Many patients are inappropriately polyuric; hyperglycemia may exacerbate this tendency. Most renal failure is due to acute tubular necrosis induced by hypovolemia, arterial hypotension, or toxic drugs, although some patients also have glomerulonephritis, renal cortical necrosis, or interstitial nephritis. Drug-induced renal damage may greatly complicate therapy, particularly when hypotensive patients are given aminoglycoside antibiotics. Nosocomial sepsis following acute renal injury is associated with a high mortality rate.

Coagulopathy Although thrombocytopenia occurs in 10–30% of patients, the underlying mechanisms are not understood. Platelet counts are usually very low (<50,000/μL) in patients with DIC; these low counts may reflect diffuse endothelial injury or microvascular thrombosis, yet thrombi have only infrequently been found on biopsy of septic organs.

Neurologic Complications Delirium (acute encephalopathy) is often an early manifestation of sepsis. Depending on the diagnostic criteria used, it occurs in 10–70% of septic patients at some point during the hospital course. When the septic illness lasts for weeks or months, "critical illness" polyneuropathy may prevent weaning from ventilatory support and produce distal motor weakness. Electrophysiologic studies are diagnostic. Guillain-Barré syndrome, metabolic disturbances, and toxin activity must be ruled out. Recent studies have documented long-term cognitive loss in survivors of severe sepsis.

Immunosuppression Patients with severe sepsis often become profoundly immunosuppressed. Manifestations include loss of delayed-type hypersensitivity reactions to common antigens, failure to control the primary infection, and increased risk for secondary infections (e.g., by opportunists such as *Stenotrophomonas maltophilia*, *Acinetobacter calcoaceticus-baumannii*, and *Candida albicans*). Approximately one-third of patients experience reactivation of herpes simplex virus, varicella-zoster virus, or cytomegalovirus infections; the latter are thought to contribute to adverse outcomes in some instances.

LABORATORY FINDINGS

Abnormalities that occur early in the septic response may include leukocytosis with a left shift, thrombocytopenia, hyperbilirubinemia, and