receptor of the human innate immune system. LPS is released from the cell membrane of gram-negative bacteria on their destruction. LPS is first bound to a carrier protein, LPS-binding protein, and the LPS monomer is then delivered to a membrane-associated, multiligand, pattern recognition receptor, CD14. LPS monomers are then passed to a soluble protein (i.e., myeloid differentiation factor 2 [MD2]) and bind to the ectodomain of TLR4. After this LPS/MD2/TLR4 complex is completed and dimerized, intracellular signaling alerts the host to the invasive infectious challenge. The pathway induces a series of phosphorylation events of adaptor proteins and signaling molecules that terminate in the activation and translocation of transcriptional activating factors such as nuclear factor-κB (NF-κB) into the nucleus. The transcription factors bind to promoter sites of the acute phase protein network, resulting in an acute outpouring of inflammatory, host defense, and coagulation components.

Other TLRs, such as TLR5 (i.e., bacterial flagella) and the TLR2/TLR1 and TLR2/TLR6 heterodimers (i.e., bacterial lipopeptides, lipoteichoic acid, and other elements of bacteria and fungi), are expressed on the cell surface of immune effector cells that recognize different molecular patterns. Nucleic acid recognition–specific TLRs reside in endosomal vacuoles, where they detect microbial DNA (TLR9), single-stranded RNA (TLR7 and TLR8), and double-stranded RNA (TLR3).

An array of complement elements, cytokines, chemokines, prostanoids (e.g., prostaglandins), vasoactive peptides, platelet-activating factor, and proteases are generated, resulting in activation of neutrophils, monocytes, macrophages, dendritic cells, lymphocytes, and endothelial cells in a combined effort to wall off the infectious process, clear the pathogens, and begin the process of tissue repair. This defense system efficiently clears pathogens from the host after local injury and the inevitable minor breaches of the epithelial barriers by microorganisms that occur over a lifetime.

If the inflammatory process is unchecked and accompanied by large numbers of pathogens or even a few highly virulent organisms (e.g., plague, tularemia, anthrax, hemorrhagic fever viruses) to which the host has no preexisting immunity, a generalized, inflammatory, and injurious process known as *sepsis* evolves over a short time, and it can be deleterious or lethal to the host. The same inflammatory response that can be lifesaving in localized infection can become life-threatening if it becomes sustained and generalized.

Endothelial membranes throughout the body are activated and become proadherent and procoagulant surfaces that promote neutrophil and platelet adherence. Neutrophils release proteases, cytokines, reactive oxygen radicals, and vasoactive prostanoids that damage endothelial cells and their function. Cytokine-inducible nitric oxide synthase is upregulated, resulting in massive generation of nitric oxide (NO). NO is a potent vasodilator, and in combination with other vasoactive peptides and phospholipid mediators, it promotes diffuse opening of capillary beds and increased permeability, with loss of intravascular fluids into the interstitial spaces. Reactive oxygen species combine with NO to generate highly injurious reactive nitrogen intermediates (e.g., peroxynitrite) that damage mitochondrial function and induce apoptosis. Systemic hypotension rapidly develops, and septic shock ensues. Immediate action by the clinician is mandatory to correct the hemodynamic status and resolve the underlying infection.

CLINICAL PRESENTATION

Despite the vast improvements in understanding the pathophysiologic basis of sepsis, clinical diagnosis remains limited to the medical history, symptomatic assessment, and nonspecific laboratory and hemodynamic criteria. Compounding the problem is the need for prompt institution of appropriate antimicrobial therapy, making early recognition of sepsis critically important. Patients with general findings as outlined in Table 89-1 should undergo thorough and prompt evaluation for a possible infectious cause, including bacterial cultures of blood and (when indicated) other body fluids. Localizing signs and symptoms should prompt a thorough physical examination and directed imaging to identify a nidus of infection. Defects of natural defensive barriers, such as transcutaneous devices or intravascular catheters, should be assessed for infection and removed if suspected to be the origin of the septic process.

Many patients have fever or chills, but older patients and those on immunomodulating medications may not mount a fever. Hypothermia portends a worse prognosis or more severe illness. Tachypnea may be an indicator of respiratory compensation for underlying metabolic acidosis or the early signs and symptoms of ARDS.

Mental status changes can result from metabolic derangements caused by sepsis, hypoglycemia, the underlying infectious process, or concomitant hypotension. This symptom can be difficult to identify in the elderly patient with dementia, and caution should be exercised in the evaluation and treatment of the otherwise stable elderly patient with possible mental status changes.

Skin findings (e.g., cellulitis, abscess) can provide clues to the cause of sepsis and may indicate the state of peripheral systemic perfusion. Several microorganisms can cause specific skin manifestations in systemic infection. *S. aureus* and streptococci can cause diffuse erythroderma, bullous lesions, or generalized desquamation. Bacteremia caused by several gram-negative organisms, including *P. aeruginosa* and enteric organisms, can result in ecthyma gangrenosum, particularly in immunocompromised patients. These lesions are round and 1 to 15 cm in diameter, and they have a central area of necrosis and peripheral erythema. Infection with *Neisseria meningitidis* can result initially in lower extremity petechiae progressing to diffuse purpura, which likely portends septic shock and a high risk of death. A similar clinical presentation can be observed in other unusual infectious diseases, such as overwhelming pneumococcal sepsis in the asplenic host or disseminated neisserial infections in patients with late complement deficiencies.

Hemodynamic instability, particularly hypotension with or without accompanying oliguria, is commonly associated with sepsis. Instability can result from poor cardiac output, intravascular fluid depletion, or low systemic vascular resistance. Hypotension can initially respond to intravenous fluid resuscitation, but in cases of severe sepsis and septic shock, it may require additional support with vasopressors. Intensive cardiac monitoring may be necessary to gauge the relative need for intravenous fluids or vasopressors after initial fluid resuscitation measures are attempted.