are the most common, and the central nervous system often is the most lethal site of infection. The number of organ systems involved plays a role, with mortality increasing as the number of dysfunctional organ systems increase.

PATHOLOGY AND IMMUNOPATHOGENESIS

The pathologic findings of fatal septic shock are often rather bland on gross examination and even histologic examination of tissue samples. The most common finding is increased tissue edema in the interstitial spaces and excess lung fluid and pleural fluid. Signs of hyaline membrane formation and fibrin deposition in the alveoli are common and indicate the fibroproliferative stage of acute respiratory distress syndrome (ARDS). Occasionally, punctate or macroscopic evidence can be detected in the adrenal tissues, as can diffuse petechiae in tissues and mucosal surfaces that indicate disseminated intravascular coagulation (DIC).

The kidneys usually appear normal, and necrosis of kidney tissues is distinctly uncommon. The term *acute tubular necrosis* is a misnomer, and the term *acute kidney injury* (AKI) is more appropriate for describing the functional and usually reversible loss of kidney function found in septic shock without accompanying evidence of glomerular or tubular necrosis.

An important finding at autopsy is identification of the infectious focus that caused septic shock. The focal infection that precipitated sepsis is readily identifiable in most deceased patients despite days to weeks of seemingly appropriate antimicrobial therapy directed against the pathogens. If careful histochemical studies are performed shortly after a patient succumbs to sepsis, excessive apoptosis (but not necrosis) of immune effector cells is identifiable in lung, spleen, lymph nodes, and hepatic tissues. Electron microscopy of tissues after death from sepsis often reveals loss of tight junctions along epithelial and endothelial surfaces. Electron microscopy also demonstrates diffuse mitochondrial swelling and degradation and clearance of intracellular organelles (i.e., autophagy).

PATHOPHYSIOLOGY OF SEPTIC SHOCK

The molecular mechanisms that underlie the basic pathophysiology of septic shock have been determined. Sepsis is triggered when a pathogen or cluster of pathogens breaches the epithelial barriers at a tissue site, evades clearance by humoral and cellular innate immune defenses, and causes an invasive infection. On entry into the host tissues, microbial pathogens are first sensed by myeloid cells of the innate immune system by pattern recognition receptors (e.g., toll-like receptors [TLRs]) on the cell surface and in endosomal compartments. TLRs detect highly conserved molecular motifs of microbes. Examples include lipopolysaccharide (LPS), the endotoxin produced by gram-negative bacteria; bacterial lipopeptides from gram-positive bacteria; β-glucans of the cell wall of fungi; viral RNA genomes and proteins; bacterial flagella; and DAMPs released from injured host cells, including intracellular structures such as histone proteins, mitochondrial DNA, and high-mobility group box 1 (Fig. 89-2).

TLRs and related intracellular pattern recognition receptors, including the inflammasome elements, retinoic acid–inducible gene 1 *(RIG1)*–like helicases, and cytoplasmic microbial TLR4, alert the host to infection. TLR4 is the long sought-after LPS

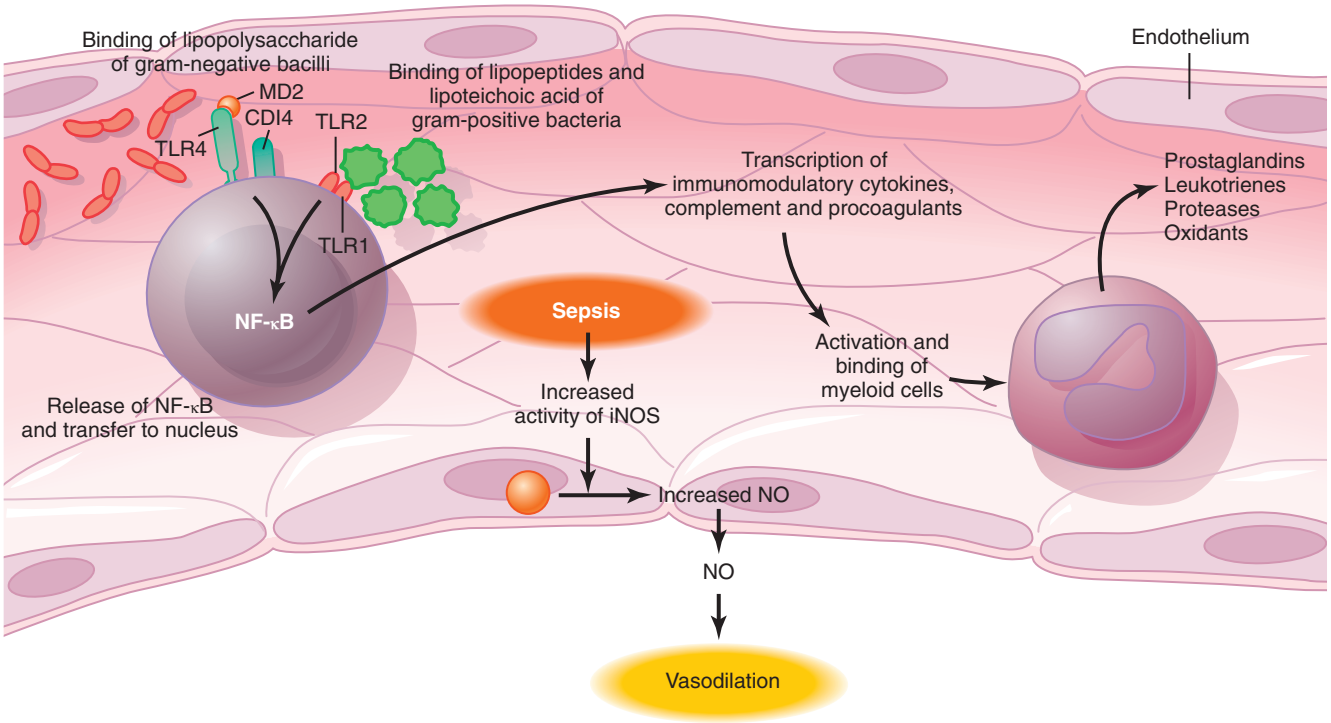

FIGURE 89-2 Immunopathogenesis of sepsis. Early recognition of bloodstream infection begins with sensing by pattern recognition receptors: toll-like receptor 4 (TLR4); cluster determinant 14 (CD14); myeloid differentiation factor 2 (MD2) for gram-negative bacterial lipopolysaccharide and TLR2 for lipoteichoic acid and other elements from gram-positive bacteria. Engagement of the TLRs by their ligands signals transcription of the acute phase response genes by the nuclear factor-κ light-chain enhancer of activated B cells (NF-κB, which is a monocyte). Septic shock is initiated by systemic release of an array of vasoactive mediators, including nitric oxide (NO) produced by cytokine-inducible NO synthase (iNOS).