TABLE 325-2 MICROORGANISMS INVOLVED IN EPISODES OF SEVERE SEPSIS AT EIGHT ACADEMIC MEDICAL CENTERS

Microorganisms	Episodes with Bloodstream Infection, % (*n* = 436)	Episodes with Documented Infection but No Bloodstream Infection, % (*n* = 430)	Total Episodes, % (*n* = 866)
Gram-negative bacteria[a]	35	44	40
Gram-positive bacteria[b]	40	24	31
Fungi	7	5	6
Polymicrobial	11	21	16
Classic pathogens[c]	<5	<5	<5

[a] Enterobacteriaceae, pseudomonads, *Haemophilus* spp., other gram-negative bacteria. [b] *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Streptococcus pneumoniae*, other streptococci, other gram-positive bacteria. [c] Such as *Neisseria meningitidis, S. pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes.*

Source: Adapted from KE Sands et al: JAMA 278:234, 1997.

EPIDEMIOLOGY

Severe sepsis is a contributing factor in >200,000 deaths per year in the United States. The incidence of severe sepsis and septic shock has increased over the past 30 years, and the annual number of cases is now >750,000 (~3 per 1000 population). Approximately two-thirds of the cases occur in patients with significant underlying illness. Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity. The rising incidence of severe sepsis in the United States has been attributable to the aging of the population, the increasing longevity of patients with chronic diseases, and the relatively high frequency with which sepsis has occurred in patients with AIDS. The widespread use of immunosuppressive drugs, indwelling catheters, and mechanical devices has also played a role. In the aforementioned international ICU prevalence study, the case–fatality rate among infected patients (33%) greatly exceeded that among uninfected patients (15%).

Invasive bacterial infections are prominent causes of death around the world, particularly among young children. In sub-Saharan Africa, for example, careful screening for positive blood cultures found that community-acquired bacteremia accounted for at least one-fourth of deaths of children >1 year of age. Nontyphoidal *Salmonella* species, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *E. coli* were the most commonly isolated bacteria. Bacteremic children often had HIV infection or were severely malnourished.

PATHOPHYSIOLOGY

Sepsis is triggered most often by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts (Table 325-2). To survive within the human body, these microbes often exploit acquired deficiencies in host defenses, indwelling catheters or other foreign matter, or obstructed fluid drainage conduits. Microbial pathogens, in contrast, can circumvent innate defenses because they (1) lack molecules that can be recognized by host receptors (see below) or (2) elaborate toxins or other virulence factors. In both cases, the body can mount a vigorous inflammatory reaction that results in sepsis or septic shock yet fails to kill the invaders. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin 1; **Chap. 172**) as well as by many pathogenic viruses.

Host Mechanisms for Sensing Microbes Animals have exquisitely sensitive mechanisms for recognizing and responding to certain highly conserved microbial molecules. Recognition of the lipid A moiety of lipopolysaccharide (LPS, also called *endotoxin*; **Chap. 145e**) is the best-studied example. A host protein (LPS-binding protein) binds lipid A and transfers the LPS to CD14 on the surfaces of monocytes, macrophages, and neutrophils. LPS then is passed to MD-2, a small receptor protein that is bound to Toll-like receptor (TLR) 4 to form a molecular complex that transduces the LPS recognition signal to the interior of the cell. This signal rapidly triggers the production and release of mediators, such as tumor necrosis factor (TNF; see below), that amplify the LPS signal and transmit it to other cells and tissues. Bacterial peptidoglycan and lipopeptides elicit responses in animals that are generally similar to those induced by LPS, although they interact with different TLRs. Having numerous TLR-based receptor complexes (10 different TLRs have been identified in humans) allows animals to recognize many conserved microbial molecules; others include lipopeptides (TLR2/1, TLR2/6), flagellin (TLR5), undermethylated DNA CpG sequences (TLR9), single-stranded RNA (TLR7, 8), and double-stranded RNA (TLR3). The ability of some TLRs to serve as receptors for host ligands (e.g., hyaluronans, heparan sulfate, saturated fatty acids, high-mobility group box 1) raises the possibility that they also play a role in producing noninfectious sepsis-like states. Other host pattern-recognition proteins that are important for sensing microbes include the intracellular NOD1 and NOD2 proteins, which recognize discrete fragments of bacterial peptidoglycan; the inflammasome, which senses some pathogens and produces interleukin (IL) 1β and IL-18; early complement components (principally in the alternative pathway); mannose-binding lectin and C-reactive protein, which activate the classic complement pathway; and Dectin-1 and complement receptor 3, which sense fungal β-glucan.

A host's ability to recognize certain microbial molecules may influence both the potency of its own defenses and the pathogenesis of severe sepsis. For example, MD-2–TLR4 best senses LPS that has a bisphosphorylated, hexaacyl lipid A moiety (i.e., one with two phosphates and six fatty acyl chains). Most of the commensal aerobic and facultatively anaerobic gram-negative bacteria that trigger severe sepsis and shock (including *E. coli*, *Klebsiella*, and *Enterobacter*) make this lipid A structure. When they invade human hosts, often through breaks in an epithelial barrier, they are typically confined to the subepithelial tissue by a localized inflammatory response. Bacteremia, if it occurs, is intermittent and low grade because these bacteria are efficiently cleared from the bloodstream by TLR4-expressing Kupffer cells and splenic macrophages. These mucosal commensals seem to induce severe sepsis most often by triggering severe local tissue inflammation rather than by circulating within the bloodstream. One exception is *Neisseria meningitidis*. Its hexaacyl LPS seems to be shielded from host recognition by its polysaccharide capsule. This protection may allow meningococci to transit undetected from the nasopharyngeal mucosa into the bloodstream, where they can infect vascular endothelial cells and release large amounts of endotoxin and DNA. Host recognition of lipid A may nonetheless influence pathogenesis, as meningococci that produce pentaacyl LPS were isolated from the blood of patients with less severe coagulopathy than was found in patients whose isolates produced hexaacyl lipid A; underacylated *N. meningitidis* LPS has also been found in many isolates from patients with chronic meningococcemia. In contrast, gram-negative bacteria that make lipid A with fewer than six acyl chains (*Yersinia pestis*, *Francisella tularensis*, *Vibrio vulnificus*, *Pseudomonas aeruginosa*, and *Burkholderia pseudomallei*, among others) are poorly recognized by MD-2–TLR4. When these bacteria enter the body, they may initially induce relatively little inflammation. When they do trigger severe sepsis, it is often after they have multiplied to high density in tissues and blood. The importance of LPS recognition in disease pathogenesis was demonstrated by engineering of a virulent strain of *Y. pestis* that makes tetraacyl LPS at 37°C to produce hexaacyl LPS; unlike its virulent parent, the mutant strain stimulated local inflammation and was rapidly cleared from tissues. These findings were subsequently replicated in *F. tularensis*. For at least one large class of microbes—gram-negative aerobic bacteria—the