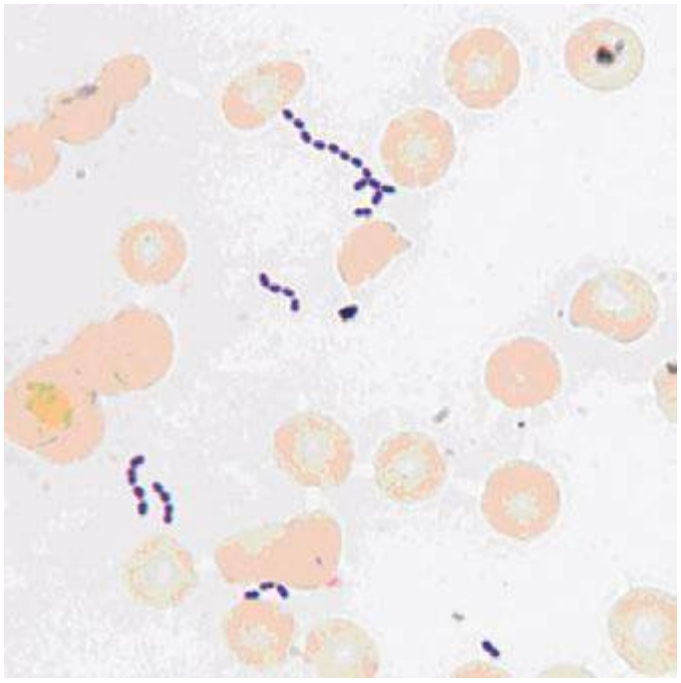

FIGURE 174-1 Gram's stain of cultured blood from a patient with enterococcal bacteremia. Oval gram-positive bacterial cells are arranged as diplococci and short chains. *(Courtesy of Audrey Wanger, PhD.)*

majority of cases are caused by two species, *E. faecalis* and *Enterococcus faecium*. Less frequently isolated species include *Enterococcus gallinarum, Enterococcus durans, Enterococcus hirae*, and *Enterococcus avium*.

PATHOGENESIS

Enterococci are normal inhabitants of the large bowel of human adults, although they usually make up <1% of the culturable intestinal microflora. In the healthy human gastrointestinal tract, enterococci are typical symbionts that coexist with other gastrointestinal bacteria; in fact, the utility of certain enterococcal strains as probiotics in the treatment of diarrhea suggests their possible role in maintaining the homeostatic equilibrium of the bowel. Enterococci are intrinsically resistant to a variety of commonly used antibacterial drugs. One of the most important factors that disrupts this equilibrium and promotes increased gastrointestinal colonization by enterococci is the administration of antimicrobial agents. In particular, antibiotics that are excreted in the bile and have broad-spectrum activity (e.g., certain cephalosporins that target anaerobes and gram-negative bacteria) are usually associated with the recovery of higher numbers of enterococci from feces. This increased colonization appears to be due not only to the simple enterococcal replacement in a "biologic niche" after the eradication of competing components of the flora, but also (at least in mice) to the suppression—upon reduction of the gram-negative microflora by antibiotics—of important immunologic signals (e.g., by the lectin RegIIIγ) that help keep enterococcal counts low in the normal human bowel. Several studies have shown that higher levels of gastrointestinal colonization are a critical factor in the pathogenesis of enterococcal infections. However, the mechanisms by which enterococci successfully colonize the bowel and gain access to the lymphatics and/or bloodstream remain incompletely understood.

Several vertebrate, worm, and insect models have been developed to study the role of possible pathogenic determinants in both *E. faecalis* and *E. faecium*. Three main groups of virulence factors may increase the ability of enterococci to colonize the gastrointestinal tract and/or cause disease. The first group, *enterococcal secreted factors*, are molecules released outside the bacterial cell that contribute to the process of infection. The best-studied of these molecules include enterococcal hemolysin/cytolysin and two enterococcal proteases (gelatinase and serine protease). Enterococcal cytolysin is a heterodimeric toxin produced by some strains of *E. faecalis* that is capable of lysing human RBCs as well as polymorphonuclear leukocytes and macrophages. *E. faecalis* gelatinase and serine protease are thought to mediate virulence by several mechanisms, including the degradation of host tissues and the modification of critical components of the immune system. Mutants lacking the genes corresponding to these proteins are highly attenuated in experimental peritonitis, endocarditis, and endophthalmitis.

A second group of virulence factors, *enterococcal surface components*, are thought to contribute to bacterial attachment to extracellular matrix molecules in the human host. Several molecules on the surface of enterococci have been characterized and shown to play a role in the pathogenesis of enterococcal infections. Among the characterized adhesins is aggregation substance of *E. faecalis*, which mediates the attachment of bacterial cells to each other, thereby facilitating conjugative plasmid exchange. Several lines of evidence indicate that aggregation substance and enterococcal cytolysin act synergistically to increase the virulence potential of *E. faecalis* strains in experimental endocarditis. The surface protein adhesin of collagen of *E. faecalis* (Ace) and its *E. faecium* homologue (Acm) recognize adhesive matrix molecules (MSCRAMMs) involved in bacterial attachment to host proteins such as collagen, fibronectin, and fibrinogen; both Ace and Acm are important in the pathogenesis of experimental endocarditis. Pili of gram-positive bacteria have been shown to be important mediators of attachment to and invasion of host tissues and are considered potential targets for immunotherapy. Both *E. faecalis* and *E. faecium* have surface pili. Mutants of *E. faecalis* lacking pili are attenuated in biofilm production, experimental endocarditis, and urinary tract infections (UTIs). Other surface proteins that share structural homology with MSCRAMMs and appear to play a role in enterococcal attachment to the host and in virulence include the *E. faecalis* surface protein Esp and its *E. faecium* homologue Esp_{fm}, the second collagen adhesin of *E. faecium* (Scm), the surface proteins of *E. faecium* (Fms), SgrA (which binds to components of the basal lamina), and EcbA (which binds to collagen type V). Additional surface components apparently associated with pathogenicity include the Elr protein (a protein from the WxL family) and polysaccharides, which are thought to interfere with phagocytosis of the organism by host immune cells. Some *E. faecalis* strains appear to harbor at least three distinct classes of capsular polysaccharide; some of these polysaccharides play a role in virulence and are potential targets for immunotherapy.

The third group of virulence factors has not been well characterized but consists of the *E. faecalis* stress protein Gls24, which has been associated with enterococcal resistance to bile salts and appears to be important in the pathogenesis of endocarditis, and the hyl_{Efm}-containing plasmids of *E. faecium*, which are transferable between strains and increase gastrointestinal colonization by *E. faecium*. In mouse peritonitis, acquisition of these plasmids increased the lethality of a commensal strain of *E. faecium*. Recently, a gene encoding a regulator of oxidative stress (AsrR) has been identified as an important virulence factor of *E. faecium*.

The ability to sequence bacterial genomes has increased our understanding of bacterial diversity, evolution, pathogenesis, and mechanisms of antibiotic resistance. The genome sequences of more than 560 enterococcal strains are currently available, and some have been entirely closed and annotated. Sequence analysis has shown that the genetic diversity of enterococci is related in large part to the acquisition of exogenous DNA and the mobilization of large chromosomal regions, resulting in recombination of the "core" genomes. In addition, analyses indicate that *E. faecium* harbors a malleable *accessory genome* incorporating a substantial content of exogenous elements, including DNA from phages. Indeed, a hospital-associated *E. faecium* clade that contains most clinical and outbreak-associated strains is the predominant genetic lineage circulating in hospitals around the world. This clade appears to be evolving rapidly, and genomic comparisons suggest that this lineage emerged 75 years ago—a time point that coincides with the introduction of antimicrobial drugs—and evolved from animal strains, not from human commensal isolates. An initial genomic