186 Diseases Caused by Gram-Negative Enteric Bacilli

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GENERAL FEATURES AND PRINCIPLES

Escherichia coli, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are gram-negative enteric bacilli that are members of the family Enterobacteriaceae. *Salmonella*, *Shigella,* and *Yersinia*, also in the family Enterobacteriaceae, are discussed in **Chaps. 190, 191, and 196**, respectively. These pathogens cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts. Increasing antimicrobial resistance in this group has put them at the forefront of an evolving public health crisis. In addition, new infectious syndromes have emerged. Therefore, a thorough knowledge of clinical presentations and appropriate therapeutic choices is necessary for optimal outcomes.

EPIDEMIOLOGY

E. coli, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are components of the normal animal and human colonic microbiota and/or the microbiota of a variety of environmental habitats, including long-term-care facilities (LTCFs) and hospitals. As a result, except for certain pathotypes of intestinal pathogenic *E. coli*, these genera are global pathogens. The incidence of infection due to these agents is increasing because of the combination of an aging population and increasing antimicrobial resistance. In healthy humans, *E. coli* is the predominant species of gram-negative bacilli (GNB) in the colonic flora; *Klebsiella* and *Proteus* are less prevalent. GNB (primarily *E. coli*, *Klebsiella*, and *Proteus*) only transiently colonize the oropharynx and skin of healthy individuals. In contrast, in LTCFs and hospital settings, a variety of GNB emerge as the dominant microbiota of both mucosal and skin surfaces, particularly in association with antimicrobial use, severe illness, and extended length of stay. LTCFs are emerging as an important reservoir for resistant GNB. This colonization may lead to subsequent infection; for example, oropharyngeal colonization may lead to pneumonia. Interestingly, the use of ampicillin or amoxicillin was associated with an increased risk of subsequent infection due to the hypervirulent variant of *Klebsiella pneumoniae* in Taiwan; this association suggests that changes in the quantity or prevalence of colonizing bacteria may be important. *Serratia* and *Enterobacter* infection may be acquired through a variety of infusates (e.g., medications, blood products). *Edwardsiella* infections are acquired through freshwater and marine environment exposures and are most common in Southeast Asia.

STRUCTURE AND FUNCTION

Enteric GNB possess an extracytoplasmic outer membrane, which consists of a lipid bilayer with associated proteins, lipoproteins, and polysaccharides (capsule, lipopolysaccharide). The outer membrane interfaces with the external environment, including the human host. A variety of components of the outer membrane are critical determinants in pathogenesis (e.g., capsule) and antimicrobial resistance (e.g., permeability barrier, efflux pumps).

PATHOGENESIS

Multiple bacterial virulence factors are required for the pathogenesis of infections caused by GNB. Possession of specialized virulence genes defines pathogens and enables them to infect the host efficiently. Hosts and their cognate pathogens have been co-adapting throughout evolutionary history. During the host-pathogen "chess match" over time, various and redundant strategies have emerged in both the pathogens and their hosts **(Table 186-1)**.

Intestinal pathogenic mechanisms are discussed below. The members of the Enterobacteriaceae family that cause extraintestinal infections are primarily extracellular pathogens and therefore share certain pathogenic features. Innate immunity (including the activities of complement, antimicrobial peptides, and professional phagocytes) and humoral immunity are the principal host defense components. Both susceptibility to and severity of infection are increased with dysfunction or deficiencies of these components. By contrast, the virulence traits of intestinal pathogenic *E. coli*—i.e., the distinctive strains that can cause diarrheal disease—are for the most part different from those of extraintestinal pathogenic *E. coli* (ExPEC) and other GNB that cause extraintestinal infections. This distinction reflects site-specific differences in host environments and defense mechanisms.

A given strain usually possesses multiple adhesins for binding to a variety of host cells (e.g., in *E. coli*: type 1, S, and F1C fimbriae; P pili). Nutrient acquisition (e.g., of iron via siderophores) requires many genes that are necessary but not sufficient for pathogenesis. The ability to resist the bactericidal activity of complement and phagocytes in the absence of antibody (e.g., as conferred by capsule or O antigen of lipopolysaccharide) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., as mediated by hemolysin in the case of *E. coli*) may facilitate spread within the host. Without doubt, many important virulence genes await identification **(Chap. 145e)**.

The ability to induce septic shock is another defining feature of these genera. GNB are the most common causes of this potentially lethal syndrome. Pathogen-associated molecular pattern molecules (PAMPs; e.g., the lipid A moiety of lipopolysaccharide) stimulate a proinflammatory host response via pattern recognition receptors (e.g., Toll-like or C-type lectin receptors) that activate host defense signaling pathways; if overly exuberant, this response results in shock **(Chap. 325)**. Direct bacterial damage of host tissue (e.g., by toxins) or collateral damage from the host response can result in the release of damage-associated molecular pattern molecules (DAMPs; e.g., HMGB1) that can propagate a detrimental proinflammatory host response.

Many antigenic variants (serotypes) exist in most genera of GNB. For example, *E. coli* has more than 150 O-specific antigens and more than 80 capsular antigens. This antigenic variability, which permits immune evasion and allows recurrent infection by different strains of the same species, has impeded vaccine development **(Chap. 148)**.

TABLE 186-1 INTERACTIONS OF EXTRAINTESTINAL PATHOGENIC *ESCHERICHIA COLI* WITH THE HUMAN HOST: A PARADIGM FOR EXTRACELLULAR, EXTRAINTESTINAL GRAM-NEGATIVE BACTERIAL PATHOGENS

Bacterial Goal	Host Obstacle	Bacterial Solution
Extraintestinal attachment	Flow of urine, mucociliary blanket	Multiple adhesins (e.g., type 1, S, and F1C fimbriae; P pili)
Nutrient acquisition for growth	Nutrient sequestration (e.g., iron via intracellular storage and extracellular scavenging via lactoferrin and transferrin)	Cellular lysis (e.g., hemolysin), multiple mechanisms for competing for iron (e.g., siderophores) and other nutrients
Initial avoidance of host bactericidal activity	Complement, phagocytic cells, antimicrobial peptides	Capsular polysaccharide, lipopolysaccharide
Dissemination (within host and between hosts)	?	Irritant tissue damage resulting in increased excretion (e.g., toxins such as hemolysin)
Late avoidance of host bactericidal activity	Acquired immunity (e.g., specific antibodies), treatment with antibiotics	?Cell entry, acquisition of antimicrobial resistance