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■ ■FURTHER READING Craig R et al: Asymptomatic infection and transmission of pertussis in households: A systematic review. Clin Infect Dis 70:152, 2020. Forsyth KD et al: Recommendations to control pertussis prioritized relative to economies: A Global Pertussis Initiative update. Vaccine 36:7270, 2018. Havers FP et al: Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: Updated recommendations of the Advi sory Committee on Immunization Practices—United States, 2019. MMWR Morb Mortal Wkly Rep 69:77, 2020. Ma L et al: Pertactin-deficient Bordetella pertussis, vaccine-driven evo lution, and reemergence of pertussis. Emerg Infect Dis 27:1561, 2021. Macina D et al: Estimating the pertussis burden in adolescents and adults in the United States between 2007 and 2019. Hum Vaccin Immunother 19:2208514, 2023. Miguelena Chamorro B et al: Bordetella bronchiseptica and Bordetella pertussis: Similarities and differences in infection, immuno-modula tion, and vaccine considerations. Clin Microbiol Rev 36:e0016422, 2023. Skoff TH: Sources of infant pertussis infection in the United States. Pediatrics 136:635, 2015. Tatti KM et al: Novel multitarget real-time PCR assay for rapid detec tion of Bordetella species in clinical specimens. J Clin Microbiol 49:4059, 2011. Winter K et al: Pertussis in California: A tale of 2 epidemics. Pediatr Infect Dis J 37:324, 2018. Wright J et al: Uptake of pertussis immunization in pregnancy and determinants of vaccination in Toronto, Canada. Vaccine 41: 6895, 2023. Thomas A. Russo, Yohei Doi

Diseases Caused by

Gram-Negative Enteric

Bacilli GENERAL FEATURES AND PRINCIPLES The postantibiotic era has begun. For most patients, this is the first time in their lives when an effective treatment for a bacterial infection may not exist. Species in the order Enterobacterales are at the forefront of this evolving public health crisis. For example, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have designated carbapenem-resistant Enterobacterales (CRE) as representing

a threat level of “urgent” and “priority one, critical.” CRE are estimated to have caused more than 100,000 deaths in 2019 globally, and the disease burden is especially high in low- and middleincome countries (e.g., Indian Subcontinent). These pathogens cause a wide variety of infections involving diverse anatomic sites, mostly in compromised hosts but also in healthy individuals. Therefore, a thor ough knowledge of clinical presentations and appropriate therapeutic choices is necessary for optimal outcomes. Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter, Morganella, Providencia, Cronobacter, and Edwardsiella are enteric gram-negative bacilli (GNB) within the order Enterobacterales that commonly cause extraintestinal infections. Salmonella, Shigella, and Yersinia, which also are in the order Enterobacterales but more commonly cause gastrointestinal infections, are discussed in Chaps. 171, 172, and 176, respectively. ■ ■EPIDEMIOLOGY E. coli, Klebsiella, Proteus, Enterobacter, Serratia, Citrobacter, Morgan ella, Providencia, Cronobacter, and Edwardsiella are components of the

normal animal and human colonic microbiota and/or the microbiota in various 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 resis tance. In healthy humans, E. coli is the predominant species of GNB in the colonic microbiota, followed by Klebsiella and Enterobacter. GNB can also colonize the oropharynx and intact skin but, in healthy individuals, tend to do so only transiently. By contrast, in LTCFs and hospital settings, a variety of GNB emerge as the dominant colonizers of both mucosal and skin epithelial surfaces, particularly in associa tion with antimicrobial use, severe illness, and extended length of stay. LTCFs are emerging as an important reservoir for resistant GNB. Such colonization with GNB may lead to subsequent extraintestinal infection; for example, oropharyngeal colonization may lead to pneu monia, and colonic/perineal colonization may lead to urinary tract infection (UTI). The use of ampicillin or amoxicillin was associated with an increased risk of subsequent infection due to the hypervirulent pathotype of Klebsiella pneumoniae in Taiwan; this association suggests that changes in the quantity or prevalence of colonizing bacteria may significantly influence the risk of infection. Serratia, Enterobacter, and, less commonly, Citrobacter infection may be acquired directly through a variety of contaminated infusates (e.g., medications, blood products, non–U.S. Food and Drug Administration [FDA]-approved stem cell products). A multistate outbreak of highly resistant Serratia due to con taminated eyedrops has occurred. Edwardsiella infections are acquired through freshwater and marine environment exposures and are most common in Southeast Asia.

CHAPTER 166 ■ ■STRUCTURE AND FUNCTION Enteric GNB possess an extracytoplasmic outer membrane consisting of a lipid bilayer with associated proteins, lipoproteins, and polysac charides (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 patho genesis (e.g., capsule, lipopolysaccharide) and antimicrobial resistance (e.g., permeability barrier, efflux pumps). In addition, secreted prod ucts play an important role in both host infection (e.g., iron acquisition molecules) and environmental niche survival and colonization (e.g., type VI secretion systems). Diseases Caused by Gram-Negative Enteric Bacilli ■ ■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 evo lutionary history. During the host–pathogen “chess match” over time, various and redundant strategies have emerged in both the pathogens and their hosts (Table 166-1). Intestinal pathogenic (diarrheagenic) mechanisms are discussed below. The members of the order Enterobacterales that cause extrain testinal infections are primarily extracellular pathogens and therefore share certain pathogenic features. The two principal components of host defense against Enterobacterales, regardless of species, are innate immunity (including intact skin and mucosal barriers; the withholding of nutrients; and the activities of complement, antimicrobial peptides, and professional phagocytes) and humoral immunity. Both suscep tibility to and severity of infection are increased with dysfunction or deficiencies of these host 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 dif ferences in host environments, defense mechanisms, and physiologic derangements that lead to disease. A given enterobacterial 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

TABLE 166-1 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 escalator 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) Intact tissue barriers Irritant tissue damage resulting in increased excretion (e.g., toxins such as hemolysin), invasion of brain endothelium Late avoidance of host bactericidal activity Acquired immunity (e.g., specific antibodies), treatment with antibiotics Cell entry, acquisition of antimicrobial resistance siderophores) requires many genes that are necessary but not sufficient for pathogenesis. The ability to resist the bactericidal activity of com plement and phagocytes in the absence of antibody (e.g., as conferred by capsule or the O antigen component of lipopolysaccharide) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., as mediated by E. coli hemolysin) may facilitate nutrient acquisition and spread within the host. Without doubt, many important virulence genes await identification. PART 5 Infectious Diseases 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 proinflam matory host response via pattern recognition receptors (e.g., Toll-like or C-type lectin receptors) that activate host defense signaling path ways; if overly exuberant, this response results in shock (Chap. 315). Direct bacterial damage of host tissue (e.g., by toxins) or collateral damage from the host response can result in the release of damageassociated 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 >150 O (somatic) antigens, 80 K (capsular) antigens, and 53 H (flagellar) antigens. This antigenic variability, which permits immune evasion and allows recurrent infection by different strains of the same species, has impeded vaccine development (Chap. 129). ■ ■INFECTIOUS SYNDROMES

Depending on both the host and the pathogen, GNB can infect nearly every organ or body cavity. E. coli can cause either intestinal or extrain testinal infection, depending on the pathotype, and Edwardsiella tarda can cause both intestinal and extraintestinal infection. Klebsiella causes primarily extraintestinal infection, but a toxin-producing variant of Klebsiella oxytoca has been associated with hemorrhagic colitis, and Providencia alcalifaciens and Escherichia albertii have been associated with gastroenteritis. E. coli and—to a lesser degree—Klebsiella account for most extrain testinal infections due to GNB. These species (for K. pneumoniae, primarily its hypervirulent pathotype) are the most virulent pathogens within this group, as demonstrated by their ability to cause severe infections in healthy, ambulatory hosts from the community. However, the other genera of GNB are also important extraintestinal pathogens, especially among LTCF residents and hospitalized patients, in large part because of the intrinsic or acquired antimicrobial resistance of these organisms and the increasing number of individuals with

compromised host defenses. The mortality rate is substantial in many GNB infections and correlates with severity of illness, underlying host status, and in some cases the antimicrobial resistance of the infecting pathogen, which can result in suboptimal therapy. Especially problem atic are pneumonia, sepsis, and septic shock (arising from any site of infection), for which the associated mortality rates are 20–60%. ■ ■DIAGNOSIS Isolation of GNB from sterile sites almost always implies infection, whereas their isolation from nonsterile sites, particularly open wounds, the respiratory tract, and urine in the presence of an indwelling cath eter, requires careful clinical correlation to differentiate colonization from infection. Clinical microbiology laboratories are increasingly replacing identification by biochemical tests with newer diagnostic methodologies such as matrix-assisted laser desorption–ionization– time-of-flight mass spectrometry (MALDI-TOF-MS), nucleic acid amplification tests (NAATs) and sequencing, and immunoassays to enhance the sensitivity, accuracy, and rapidity of reporting on patho gen identification and resistance genes. This information can be used to increase the timeliness of initiation and/or the accurate selection of empirical antimicrobial therapy, thereby improving outcomes. These new diagnostic modalities have also resulted in the identification from clinical specimens of unfamiliar species (e.g., K. grimontii, Enterobacter hormaechei). It is best to assume such isolates possess a similar patho genic potential as their more familiar counterparts until more data become available. TREATMENT Principles Guiding Treatment in the Era of Increasing Antimicrobial Resistance (See also Chap. 149) Initiation of appropriate empirical anti microbial therapy early in the course of infections due to GNB (particularly the more serious ones) leads to improved outcomes. The ever-increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB; the lag between published and current resistance rates; and variations in antimicrobial suscep tibility by species, geographic location, regional antimicrobial use, and hospital site (e.g., intensive care units [ICUs] vs wards) neces sitate familiarity with evolving patterns of antimicrobial resistance for the selection of appropriate empirical therapy. Patient factors predictive of resistance in a given isolate include recent antimicrobial use, a health care association (e.g., recent or ongoing hospitalization, dialysis, residence in an LTCF, transplant, hematologic malignancy), or international travel (e.g., to Asia, Latin America, Africa, Eastern Europe). Of concern are an increasing number of reports of resistant Enterobacterales causing infections in ambulatory patients without known risk factors. In this era of increasing antimicrobial resistance, it is critical to culture the primary site of infection before initiating antimicrobial therapy and, for systemically ill patients, to obtain blood cultures. In vitro testing may not always detect antimicrobial resistance; therefore, it is important to assess the patient’s clinical response to treatment. Moreover (see discussion of AmpC β-lactamases below),

resistance may emerge during therapy. In addition, drainage of abscesses, resection of necrotic tissue, and removal of infected for eign bodies, sometimes referred to collectively as “source control,” are often required for cure. For appropriately selected patients, it may be prudent initially, pending antimicrobial susceptibility results, to use two potentially active agents to increase the likelihood that at least one agent will be active against the patient’s organism. If broad-spectrum treatment has been initiated, it is important to switch to the most appropriate narrower-spectrum agent once antimicrobial suscep tibility results become available. Such responsible antimicrobial stewardship should help disrupt the ever-escalating cycle of selec tion for increasingly resistant bacteria, plus decrease the likelihood of Clostridioides difficile infection, decrease costs, and maximize

the useful longevity of available antimicrobial agents. Likewise, it is important to avoid treatment of patients who are colonized but not infected (e.g., who have a positive sputum culture without evidence of pneumonia, or a positive urine culture without clinical manifes tations of UTI). At present, the most reliably and broadly active antimicrobial agents in vitro against Enterobacterales are the carbapenems (except ing imipenem, to which Proteeae [Proteus, Morganella, Providencia] are intrinsically resistant); the aminoglycoside amikacin (excepting the Proteeae); the fourth-generation cephalosporin cefepime; the β-lactamase inhibitor combination agents piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, meropenemvaborbactam, and imipenem/cilastatin-relebactam; and the novel cephalosporin-siderophore cefiderocol. A limitation of imipenem/ cilastatin-relebactam; the tetracycline derivatives tigecycline, oma dacycline, and eravacycline; and the polymyxins B and E (colistin) (which are otherwise very active) is their poor activity against

Proteeae and Serratia. Furthermore, the tetracycline derivatives achieve suboptimal concentrations at several anatomic sites (including urine and blood). Clinical data are limited for cefidero col outside of UTIs and hospital-acquired ventilator-associated bacterial pneumonias; thus, caution is in order for serious infec tions at other sites. The number of antimicrobial agents active against certain strains of Enterobacterales is shrinking, and truly pandrug-resistant GNB exist. Accordingly, the currently available antimicrobial drugs must be used judiciously. Extensive resistance to available agents may leave the clinician with few or no ideal therapeutic options. However, use of a regimen that considers the site of infection, achievable drug levels at that site (e.g., higher concentrations of many agents in urine), and pharmacodynamically guided administration strategies (e.g., pro longed infusion of β-lactam agents to maintain drug levels above the minimal inhibitory concentration [MIC]) may increase the chance for a successful outcome. Point-of-care, NAAT-based identification of resistance mechanisms in GNB is becoming available and will enable a strain-specific, patient-specific, precision medicine–based treatment approach that would be predicted to improve outcome. GNB are commonly involved in polymicrobial infections, in which the role of each individual pathogen is uncertain (Chap. 182). Although some GNB are more pathogenic than others, it is usu ally prudent, if possible, to design an antimicrobial regimen active against all the GNB identified, because each is typically capable of pathogenicity in its own right. For patients treated initially with a broad-spectrum empirical regimen, the regimen should be deescalated as expeditiously as possible once susceptibility results are known and the patient has responded to therapy. Treatment duration is best individualized based on underlying host status and site of infection. However, for selected non–critically ill patients with source control and a satisfactory clinical response to therapy, 7 days of treatment may suffice for many infections.

ANTIMICROBIAL TREATMENT AND RESISTANCE MECHANISMS The most common resistance mechanisms possessed by Enterobac terales are summarized in Table 166-2. Enzymatic hydrolysis (e.g., β-lactamases, of which >3000 variants have been described) and modification of antimicrobials are the major mediators of resistance in GNB and will be discussed below. Importantly, it is becoming increasingly recognized that MDR and XDR GNB often possess multiple plasmids and genes that encode for multiple β-lactamases. Broad-spectrum β-lactamases mediate resistance to many peni cillins and first-generation cephalosporins and are frequently expressed in enteric GNB. These enzymes are inhibited by all avail able β-lactamase inhibitors (e.g., clavulanate, sulbactam, tazobac tam, avibactam, relebactam, vaborbactam). In their wild-type form, they do not hydrolyze third- and fourth-generation cephalosporins or cephamycins (e.g., cefoxitin). Extended-spectrum β-lactamases (ESBLs) are modified broadspectrum enzymes that hydrolyze third-generation cephalosporins,

TABLE 166-2 Common Antimicrobial Resistance Mechanisms Possessed by the Enterobacterales ANTIMICROBIALS MOST SIGNIFICANTLY AFFECTED COMMON MEDIATORS

OF RESISTANCE MECHANISM Efflux Tetracyclines, fluoroquinolones (FQ) Efflux pumps Decreased permeability Fosfomycin Alterations in uptake system Target site alteration or overproduction FQ, trimethoprimsulfamethoxazole (TMPSMX), and polymyxins DNA gyrase or topoisomerase IV for FQ; enzymes for folic acid synthesis for TMP-SMX Lipid A for polymyxins Enzymatic hydrolysis of antimicrobials Penicillins, cephalosporins, cephamycins, carbapenems Broad-spectrum β-lactamases (e.g., TEM, SHV) ESBLs (e.g., CTX-M, modified TEM and SHV) AmpC β-lactamases Carbapenemases (e.g., serinebased KPC, OXA; metallobased NDM, VIM, IMP) Enzymatic modification of antimicrobials Aminoglycosides AAC, ANT, APH Abbreviations: AAC, N-acetyltransferases; ANT, O-adenylyltransferases; APH, O-phosphotransferases; CTX, cefotaxime β-lactamase; ESBL, extendedspectrum β-lactamase; IMP, active on imipenem; KPC, Klebsiella pneumoniae carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; SHV, sulfhydryl reagent variable β-lactamase; TEM, Temoniera β-lactamase; VIM, Verona integron-mediated metallo-β-lactamase. CHAPTER 166 aztreonam, and (in some instances) fourth-generation cephalo sporins, in addition to the drugs hydrolyzed by broad-spectrum β-lactamases. GNB that produce ESBLs may also exhibit porin mutations that result in decreased uptake of relevant β-lactam agents (cephalosporins, β-lactam/β-lactamase inhibitor combina tions, and carbapenems), further reducing susceptibility to these agents. The prevalence of acquired ESBL production, particularly of CTX-M-type enzymes, is increasing in GNB worldwide, largely due to the presence of the corresponding genes on transferable plas mids, which also variably confer or are associated with resistance to fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, tetracyclines, and (more recently) fosfomycin. To date, ESBLs are most prevalent in E. coli (especially ST131), K. pneumoniae, and K. oxytoca, but these enzymes can occur in all species of Enterobacterales. The approximate regional prevalence of ESBL-producing GNB currently follows a descending gradient as follows: China > Eastern Europe > other parts of Asia (e.g., India)

> “ Latin America and Africa > Western Europe, the United States, Canada, and Australia. Travel to high-prevalence regions increases the likelihood of colonization with these strains. The incidence of community-acquired infections

> due to ESBL-producing Entero bacterales has increased worldwide, including in the United States. Diseases Caused by Gram-Negative Enteric Bacilli Carbapenems are the most reliably active β-lactam agents against ESBL-producing strains. Piperacillin-tazobactam, when active in vitro, has been used as a carbapenem-sparing alternative, but recent data from the MERINO trial do not support its use for bloodstream infections. Ceftazidime-avibactam, ceftolozane-tazobactam (less active against Klebsiella, Enterobacter, and Citrobacter) are also active against most ESBL-producing strains but have limited clinical data that support potential utility. The roles for tigecycline, eravacy cline, and omadacycline are unclear despite these agents' excellent in vitro activity against most Enterobacterales; however, they are inactive against Proteus, Morganella, Providencia, and Serratia. Oral options for the treatment of ESBL-producing strains are very limited. Fosfomycin, nitrofurantoin (for E. coli, 75–90% sus ceptible), pivmecillinam (recently approved in the United States), and omadacycline are the most reliably active agents. Older tetra cyclines (e.g., doxycycline and minocycline) also are often active,

although urine levels may be insufficient and clinical experience with gram-negative infections is limited.

AmpC β-lactamases, when induced or stably derepressed to high levels of expression, confer resistance to the same substrates as do ESBLs plus to the cephamycins (e.g., cefoxitin and cefotetan), except to the fourth-generation cephalosporins. The genes encod ing these enzymes are primarily chromosomal and therefore may not exhibit the linked resistance to TMP-SMX, aminoglycosides, and tetracyclines that is common with ESBLs. These enzymes are problematic for the clinician: resistance may develop dur ing therapy with third-generation cephalosporins and result in clinical failure, particularly in the setting of bacteremia. Although chromosomal AmpC β-lactamases are present in nearly all mem bers of the order Enterobacterales (with the notable exceptions of

K. pneumoniae, K. oxytoca, and Proteus mirabilis), the risk of clinically significant induction of high-level expression or selection of stably derepressed mutants with cephalosporin treatment is not uniform across species, being greatest with Enterobacter cloacae, Klebsiella (formerly Enterobacter) aerogenes, Citrobacter freundii, and Hafnia alvei, and less with Serratia marcescens, Providencia, and Morganella morganii. In addition, rare strains of E. coli, K. pneumoniae, and other Enterobacterales have acquired plasmids that contain AmpC β-lactamase genes. For AmpC-producing strains, carbapenems are an appropriate treatment option, especially for severely ill patients. Meta-analyses support piperacillin-tazobactam as a possible option. The fourthgeneration cephalosporin cefepime may be an appropriate option if the concomitant production of an ESBL can be excluded (a task that currently exceeds the capability of most clinical microbiol ogy laboratories) and source control is achieved. Ceftazidimeavibactam and cefiderocol are active in vitro, but clinical data are limited. Other carbapenem-sparing alternatives to consider if isolates are susceptible in vitro include fluoroquinolones, TMPSMX, and aminoglycosides. Tigecycline, eravacycline, and oma dacycline are active in vitro (except against Proteus, Morganella, Providencia, and Serratia). PART 5 Infectious Diseases Carbapenemases of Ambler class A (serine-

β-lactamases; e.g., K. pneumoniae carbapenemase [KPC]) and class B (metallo-βlactamases [MBLs]; e.g., New Delhi metallo-β-lactamase [NDM], Verona integron-mediated metallo-β-lactamase [VIM], imipen emase [IMP]) confer resistance to the same drugs as do ESBLs, plus to cephamycins and carbapenems. By contrast, Ambler class D carbapenemases (serine-β-lactamases; e.g., oxacillinase-48 [OXA-48]) hydrolyze carbapenems and penicillins, but they have minimal activity against extended-spectrum cephalosporins. As with ESBLs, carbapenemase-encoding genes may be present on transferable plasmids, which often encode linked resistance to fluoroquinolones, TMP-SMX, tetracyclines, and aminoglycosides. Transposon-mediated spread (e.g., Tn4401 for KPC) also is impor tant. Although all major carbapenemases have been described around the globe, KPC is most common in the Americas, NDM in Asia, and OXA in Europe. Asymptomatic intestinal carriage of producing bacteria may facilitate spread. Carbapenemase-producing Enterobacterales (CPE) are most prevalent in K. pneumoniae, followed by Enterobacter spp. and

E. coli, but have been described in nearly all members of the order. M. morganii, Proteus, and Providencia exhibit intrinsic low-level imipenem resistance. A variety of genotypic and phenotypic meth ods can detect carbapenemase genes or activity, which could inform epidemiologic surveillance, infection control efforts, antimicrobial stewardship, and treatment decisions, especially if susceptibility data for selected agents are not available. For the treatment of infections due to Enterobacterales that produce class A or D carbapenemases (serine-β-lactamases; KPC, OXA), ceftazidime-avibactam is emerging as a first-line agent particularly for bacteremia, but suboptimal efficacy has been observed with pneumonia and in patients on renal replacement therapy, and resistance has developed in up to 10% of cases. Clini cal success against KPC-producing CRE has also been reported

for meropenem-vaborbactam and, to a lesser extent, imipenem/ cilastatin-relebactam; unlike ceftazidime-avibactam, however, neither of these agents is active against OXA-producing CRE. Ceftazidime, cefepime, and aztreonam are active against OXA48-producing CRE, unless other enzymes such as ESBL an AmpC are co-produced. Treatment of infections due to class B MBL–producing CRE is more challenging. The polymyxins B and E currently constitute one of the last lines of defense against strains that produce MBLs (e.g., NDM). However, these agents' nephrotoxicity and neurotoxicity potential, their limited clinical efficacy, and the recent emergence of the polymyxin resistance threaten their utility. Aztreonam is stable against MBLs but is hydrolyzed by ESBLs and AmpC β-lactamases, which are often coproduced in XDR strains. Ongoing clinical trials are assessing aztreonam plus avibac tam, a promising combination with in vitro activity against class A, B, and D enzymes, for the treatment of CRE strains that produce MBLs like NDM. A currently available workaround involving approved drugs is co-administration of ceftazidime-avibactam and aztreonam; avibactam protects aztreonam from hydrolysis from ESBLs and AmpC β-lactamases. Cefiderocol is active in vitro against most strains producing KPC, MBLs, and OXA-48 (i.e., classes A, B, and D enzymes); clinical trials suggest that it may be as efficacious for serious CRE infections as the standard of care, but real-world data are limited. Although tigecycline, eravacycline, and omadacycline are active in vitro, pharmacokinetic-pharmacodynamic limitations exist, and along with the polymyxins, they exhibit poor activity against the tribe Proteeae and Serratia. Aminoglycosides, especially amikacin, may have some utility for combination therapy. Fosfomycin is often active in vitro, but clinical data in the treatment of serious infections due to CPE are limited and resistance may develop with monotherapy. Carbapenem resistance in the absence of carbapenemases can occur in the presence of ESBLs or

AmpC β-lactamase production in combination with porin mutations (non-CP-CRE); however, most laboratories will not be able to differentiate CPE from non-CP-CRE. The non-CP-CRE phenotype is most commonly seen in E. coli and Enterobacter spp. In general, resistance to noncarbapenem antimi crobial classes is less, but data are limited on the optimal manage ment approach for non-CP-CRE. Resistance to classic β-Lactamase inhibitors is an uncommon (4% of E. coli/K. pneumoniae blood isolates) but increasingly recog nized phenotype that is characterized by resistance to β-lactamase inhibitors but not to third-generation cephalosporins. This mecha nism of resistance is distinct from production of ESBLs, AmpC β-lactamases, and carbapenemases, and it is still being delineated. Limited evidence suggests that ceftriaxone is an appropriate treat ment option for such strains. Resistance to newer β-lactamase inhibitors, especially avibactam, is increasingly reported in KPCproducing CPE and is due to mutations leading to structural modi fications of the KPC enzyme. These strains remain susceptible to meropenem-vaborbactam. Fluoroquinolone resistance is usually due to alterations in or protection of the target sites in DNA gyrase and topoisomerase IV, with or without decreased permeability and active efflux. Fluo roquinolone resistance is increasingly prevalent among GNB and is associated with resistance to other antimicrobial classes; for example, 20–80% of ESBL-producing enteric GNB are also resis tant to fluoroquinolones. At present, fluoroquinolones should be considered unreliable as empirical therapy for GNB infections in critically ill patients. Aminoglycoside resistance in Enterobacterales is conferred via enzymatic modification by N-acetyltransferases, O-adenylyltrans ferases, or O-phosphotransferases, which in turn affects ribosomal binding. Amikacin is less affected by these transferases than gen tamicin and tobramycin and therefore is generally more active. A yet uncommon resistance mechanism involves acquired 16S ribosomal RNA methyltransferases, which prevent all parenterally

administered aminoglycosides from binding to their target ribo somes. To date, these methyltransferases are most common in strains that produce MBLs (e.g., NDM). ■ ■PREVENTION (See also Chap. 147) Certain measures are broadly applicable for decreasing infection risk. Antimicrobial stewardship programs should be instituted to facilitate appropriate antimicrobial use, which will minimize the development of resistance. Diligent adherence to hand hygiene protocols by health care personnel and cleaning/disinfection or single-patient use of objects that come into contact with patients (e.g., stethoscopes and blood pressure cuffs) are essential. Indwelling devices (e.g., urinary and intravascular catheters) should be used only when necessary and inserted according to an appropriate protocol; protocols for daily-use evaluation and prompt removal should be implemented. Multiuse medication vials should be avoided if possible. Oral application of chlorhexidine decreases the incidence of pneumo nia among patients on ventilators. Increasing data support the imple mentation of universal decolonization (e.g., chlorhexidine bathing) to prevent infection in ICU patients or nursing home residents. The public health threat from CRE has resulted in additional recommen dations, especially for carbapenemase-producing CRE, which are an even greater concern. These recommendations include contact precau tions for patients colonized or infected with CRE, notification to the receiving facility from facilities transferring such a patient, and daily environmental cleaning. Screening of contacts and active surveillance for these bacteria also may be appropriate. ESCHERICHIA COLI INFECTIONS All E. coli strains share a core genome of ~2,000 genes. In con trast, an E. coli strain’s ability to cause infection and the nature of such infections are defined largely by accessory (i.e., noncore, nonessential) genes that encode various virulence factors. The compo sition of the E. coli accessory genome is continuously in flux, as dem onstrated by the recent evolution of Shiga toxin–producing enteroaggregative E. coli. ■ ■COMMENSAL STRAINS Commensal E. coli variants are an important constituent of the normal

intestinal microbiota that confer benefits to the host (e.g., resistance to colonization with pathogenic organisms). Such strains generally lack the specialized virulence traits that enable extraintestinal and intestinal pathogenic E. coli strains to cause disease outside and within the gastrointestinal tract, respectively. However, even commensal

E. coli strains can be involved in extraintestinal infections in the pres ence of an aggravating factor, such as a foreign body (e.g., a urinary catheter), host compromise (e.g., local anatomic or functional abnor malities [including urinary or biliary tract obstruction] or systemic TABLE 166-3 Intestinal Pathogenic Escherichia coli PATHOTYPE EPIDEMIOLOGY CLINICAL SYNDROMEa DEFINING MOLECULAR TRAIT STEC/EHEC/ ST-EAEC Food, water, person-to-person; all ages, industrialized countries Hemorrhagic colitis, hemolyticuremic syndrome ETEC Food, water; young children in and travelers to developing countries Traveler’s diarrhea Heat-stable and labile enterotoxins, colonization factors EPEC Person-to-person; young children and neonates in developing countries Watery diarrhea, persistent diarrhea EIEC Food, water; children in and travelers to developing countries Watery diarrhea, occasionally dysentery EAEC ?Food, water; children in and travelers to developing countries; all ages, industrialized countries Traveler’s diarrhea, acute diarrhea, persistent diarrhea aClassic syndromes; see text for details on disease spectrum. bPathogenesis involves multiple genes, including genes in addition to those listed. Abbreviations: EAEC, enteroaggregative E. coli; EHEC, enterohemorrhagic E. coli; EIEC, enteroinvasive E. coli; EPEC, enteropathogenic E. coli; ETEC, enterotoxigenic E. coli; ST-EAEC, Shiga toxin–producing enteroaggregative E. coli; STEC, Shiga toxin–producing E. coli.

immunocompromise), or an inoculum that is large or contains a mixture of bacterial species (e.g., fecal contamination of the peritoneal cavity).

■ ■EXTRAINTESTINAL PATHOGENIC STRAINS ExPEC strains are the most common enteric GNB to cause communityacquired and health care–associated bacterial infections. The emerging propensity of these strains to acquire new mechanisms of antimicrobial resistance (e.g., FQ resistance mutations, ESBLs, carbapenemases) poses novel challenges in managing ExPEC infection. Several ExPEC clonal groups (e.g., sequence types [STs] ST131, ST95, ST69, ST73) are recognized to have undergone global dissemination. The mecha nisms underlying the epidemiologic success of such disseminated lineages remain an area of active investigation. In the case of ST131, efficient human-to-human transmission followed by colonization and long-term persistence within the intestinal microbiota appears to be a critical factor. Although acquisition of ESBL-producing E. coli from the food chain has been described, this appears to occur relatively uncommonly. Like commensal E. coli (but unlike intestinal pathogenic E. coli), ExPEC strains are often found in the intestinal microbiota of healthy individuals and, except for rare chimeric ExPEC/intestinal pathogenic E. coli strains, do not cause gastroenteritis in humans. Entry from their site of colonization (e.g., the colon, vagina, or oropharynx) into a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs) is the rate-limiting step for infection. ExPEC strains have acquired accessory genes encoding diverse virulence factors that enable the bacteria to cause infections outside the gastrointestinal tract in both normal and compromised hosts (Table 166-1). These virulence genes define ExPEC and, for the most part, are distinct from the viru lence genes that enable intestinal pathogenic strains to cause diarrheal disease (Table 166-3). All age groups, all types of hosts, and nearly all organs and anatomic sites are susceptible to infection by ExPEC. Even previously healthy hosts can become severely ill or die when infected with ExPEC;

however, adverse outcomes are more common among hosts with comorbid illnesses and host defense abnormalities. The diversity and the medical and economic impact of ExPEC infections are evident from consideration of the following specific syndromes. CHAPTER 166 Diseases Caused by Gram-Negative Enteric Bacilli
Extraintestinal Infectious Syndromes • URINARY TRACT INFECTION The urinary tract is the site most frequently infected by ExPEC. UTI is an exceedingly common infection among ambulatory patients, accounting for 1% of ambulatory care visits in the United States and second only to lower respiratory tract infection among infections responsible for hospitalization. UTIs are best considered by clinical syndrome (e.g., cystitis, pyelonephritis, catheter-associated UTI) and within the context of specific hosts (e.g., premenopausal women, immunocompromised hosts; Chap. 140). E. coli is the single most common pathogen for all UTI syndrome/host group combinations. RESPONSIBLE GENETIC ELEMENTb Shiga toxin Lambda-like Stx1- or Stx2encoding bacteriophage Virulence plasmid(s) Localized adherence, attaching and effacing lesion on intestinal epithelium EPEC adherence factor plasmid pathogenicity island (locus for enterocyte effacement [LEE]) Invasion of colonic epithelial cells, intracellular multiplication, cell-to-cell spread Multiple genes contained primarily in a large virulence plasmid Aggregative/diffuse adherence, virulence factors regulated by AggR Chromosomal or plasmidassociated adherence and toxin genes

Each year in the United States, E. coli causes 80–90% of the estimated 6–8 million episodes of cystitis that occur in ambulatory, premeno pausal women with an anatomically and functionally normal urinary tract (i.e., uncomplicated cystitis). Furthermore, 20% of women with an initial cystitis episode develop frequent recurrences.

Uncomplicated cystitis, the most common acute UTI syndrome, is characterized by dysuria, urinary frequency and urgency, and supra pubic pain. Progression to more severe infection is rare; the natural history is slow spontaneous symptom resolution, which antimicrobial therapy hastens. Fever and/or back pain suggest progression to pyelo nephritis. Even when pyelonephritis is treated effectively, fever may take 5–7 days to resolve completely. Persistently elevated or increasing fever, flank pain, and neutrophil counts should prompt evaluation for intrarenal or perinephric abscess and/or obstruction. Pyelonephritis uncommonly causes renal parenchymal damage and loss of renal func tion, primarily in association with urinary obstruction, which can be preexisting or, rarely, occurs de novo in diabetic patients who develop renal papillary necrosis due to kidney infection. Pregnant women are at unusually high risk for developing pyelonephritis, which can adversely affect the outcome of pregnancy. As a result, prenatal screening for and treatment of asymptomatic bacteriuria during pregnancy are standard. Prostatic infection (prostatitis), a potential complication of UTI in men, can present either acutely (severe), which is rare, or in a chronic manner (recurrent cystitis), which is much more common. Acute pyelonephritis, acute prostatitis, and other systemic illnesses due to UTI can be designated collectively as urosepsis, febrile UTI, or systemic UTI, and may or may not be accompanied by bacteremia. The diagno sis and treatment of UTI, as detailed in Chap. 140, should be tailored to the individual host, the nature and site of infection, and local patterns of antimicrobial susceptibility. PART 5 Infectious Diseases ABDOMINAL AND PELVIC INFECTION The abdomen/pelvis is the second most common site of extraintestinal infection due to E. coli. A wide variety of clinical syndromes occur in this location, includ ing acute peritonitis secondary to fecal contamination, spontane ous bacterial peritonitis, dialysis-associated peritonitis, diverticulitis, appendicitis, intraperitoneal or visceral abscesses (hepatic, pancreatic, splenic), infected pancreatic pseudocysts, and septic cholangitis and/or

cholecystitis. In intraabdominal infections, E. coli can be isolated either alone or, as occurs more often, in combination with other facultative and/or anaerobic members of the intestinal microbiota (Chap. 137). PNEUMONIA E. coli is not usually considered an important cause of pneumonia (Chap. 131). Indeed, enteric GNB account for only 1–3% of cases of community-acquired pneumonia, in part because these organisms colonize the oropharynx only transiently in a minority of healthy individuals. However, rates of oral colonization with E. coli and other GNB increase with severity of illness and antibiotic use. Consequently, GNB are a more common cause of pneumonia among residents of LTCFs and of hospital-acquired pneumonia (Chap. 147), particularly among postoperative and ICU patients (e.g., ventilatorassociated pneumonia). Pulmonary infection is usually acquired by small-volume aspira tion but occasionally occurs via hematogenous spread, in which case multifocal nodular infiltrates can be seen. Tissue necrosis, probably due in part to bacterial cytotoxins, is common. Despite significant institutional variation, E. coli is generally the third or fourth most commonly isolated type of GNB in hospital-acquired pneumonia, accounting for 5–8% of episodes in both U.S.-based and Europe-based studies. Regardless of the host, pneumonia due to ExPEC is a serious disease, with high crude and attributable mortality rates (20–60% and 10–20%, respectively). MENINGITIS (See also Chap. 143) E. coli is one of the leading causes of neonatal meningitis, together with group B Streptococcus. Most E. coli strains that cause neonatal meningitis possess the K1 capsular antigen and derive from a limited number of meningitis-associated clonal groups (ST95, ST59, ST62). Ventriculomegaly occurs com monly. After the first month of life, E. coli meningitis is uncommon and usually accompanies surgical or traumatic disruption of the meninges or hepatic cirrhosis. In patients with cirrhosis who develop meningitis,

the meninges are presumably seeded due to poor hepatic clearance of portal vein bacteremia. CELLULITIS/MUSCULOSKELETAL INFECTION E. coli contributes fre quently to infections of decubitus ulcers and occasionally to infections of lower-extremity ulcers and wounds in diabetic patients and other hosts with neurovascular compromise. Osteomyelitis secondary to contiguous spread can occur in these settings. E. coli also causes cel lulitis or infections of burn sites and surgical wounds (accounting for ~10% of surgical site infections), particularly when the infection origi nates close to the perineum. E. coli causes hematogenously acquired osteomyelitis, especially of vertebral discs and bodies, accounting for up to 10% of cases in some series (Chap. 136). E. coli occasionally causes orthopedic device–associated infection or septic arthritis and rarely causes hematogenous myositis. Myositis or fasciitis of the thigh due to E. coli should prompt an evaluation for an abdominal source with contiguous spread. ENDOVASCULAR INFECTION Despite being one of the most common causes of bacteremia, E. coli rarely seeds native heart valves. When the organism does infect native valves, it usually does so in the setting of prior valvular disease. E. coli infections of aneurysms, the portal vein (pylephlebitis), and vascular grafts are uncommon. MISCELLANEOUS INFECTIONS E. coli can cause infection in nearly every organ and anatomic site. It occasionally causes postoperative mediastinitis or complicated sinusitis and uncommonly causes endo phthalmitis, ecthyma gangrenosum, or brain abscess. BACTEREMIA E. coli bacteremia can arise from infection at any extrain testinal site. In addition, E. coli bacteremia can arise from percutaneous intravascular devices, transrectal prostate biopsy, and the increased intes tinal mucosal permeability seen in neonates and patients with advanced cirrhosis, neutropenia, chemotherapy-induced mucositis, trauma, and extensive burns. E. coli bacteremia due to an ESBL-producing strain also has been reported after fecal microbiota transplant in patients with increased mucosal permeability. Roughly equal proportions of E. coli bacteremia cases originate in the community and in health care settings. Isolation of E. coli from the blood is almost always clinically

significant and may be accompanied by the sepsis syndrome (dysfunction of at least one organ or system) or septic shock (Chap. 315). The urinary tract is the most common source for E. coli bacteremia, accounting for one-half to two-thirds of episodes. Bacteremia from a urinary tract source is particularly common among patients with pyelonephritis, urinary tract obstruction, or urinary instrumentation in the presence of infected urine. The abdomen is the second most common source, accounting for ~25% of episodes. Although many of these episodes result from biliary obstruction (stones, tumor) and overt bowel disruption, which typically are readily apparent, some abdominal sources (e.g., abscesses) are remarkably silent clinically and require identification via imaging studies (e.g., computed tomogra phy). Therefore, especially given the high prevalence of asymptomatic bacteriuria among elderly and functionally compromised individuals, the physician should be cautious in attributing E. coli bacteremia to a urinary source in the absence of characteristic signs and symptoms of UTI. Soft tissue, bone, pulmonary infections, and intravascular cath eter infections are other sources of E. coli bacteremia. Diagnosis Strains of E. coli that cause extraintestinal infections usu ally grow both aerobically and anaerobically within 24 h on standard diagnostic media and are identified readily by the clinical microbiology laboratory according to routine biochemical criteria. More than 90% of ExPEC strains are rapid lactose fermenters and are indole-positive. However, MALDI-TOF MS is increasingly replacing biochemical methods. TREATMENT Extraintestinal E. coli Infections E. coli does not possess clinically significant intrinsic resistance to antimicrobials; however, increasing acquired resistance is

making treatment problematic. Although geographic differences exist, in general, the prevalence of resistance is >20% for ampi cillin, amoxicillin-clavulanate, ampicillin-sulbactam, cefazolin, TMP-SMX, and fluoroquinolones, even in community-acquired infections. This resistance precludes empirical use of these agents for serious infections. Travel outside of the United States, prior exposure to an antimicrobial agent, or exposure to a health care setting further increases the likelihood of resistance. Fortunately,

> 90% of isolates that cause uncomplicated cystitis remain suscep tible to nitrofurantoin and fosfomycin. From 2015 to 2017, the U.S. National Healthcare Safety Network (USNHSN) identified 24% of E. coli clinical isolates as ESBLproducers. Higher prevalences are reported from Asia, Eastern Europe, South America, and Africa; prevalence is also greater in isolates from health care settings, especially LTCFs. Unfortunately, community-acquired UTIs caused by E. coli strains that produce CTX-M ESBLs are increasingly common. Oral treatment options for ESBL-producers are limited. However, in vitro and limited clini cal data indicate that fosfomycin, pivmecillinam, and nitrofurantoin are most active and can be used for cystitis (but not pyelonephritis); omadacycline is an option for pulmonary of soft-tissue infection. For parenteral therapy of carbapenem-susceptible strains, the most predictably active agents (>90%) include carbapenems, ami kacin, ceftazidime-avibactam, ceftolozane-tazobactam, piperacillintazobactam, polymyxins, cefiderocol, tigecycline, eravacycline, and omadacycline with the caveat that site-specific concentration and potential efficacy are agent dependent. Treatment of carbapenemaseproducing strains is dependent on the class of enzyme produced

(see “Carbapenemase” above). Uncertainty exists on the optimal treatment for non-CP-CR E. coli. Empirical treatment decisions for critically ill patients should be dictated by local susceptibility patterns and patient-specific risk fac tors (1.2% prevalence from the USNHSN 2015−2017 data). Equally important as prompt institution of effective empirical therapy for seriously ill patients is use of appropriate narrower-spectrum agents for definitive therapy whenever possible and avoidance of treatment for patients who are colonized but not infected. ■ ■INTESTINAL PATHOGENIC STRAINS Pathotypes Certain strains of E. coli are capable of causing diar rheal disease. (Other important intestinal pathogens are discussed in Chaps. 138, 139, and 171–174.) At least in the industrialized world, intestinal pathogenic E. coli strains are rarely encountered in the fecal flora of healthy persons, and instead appear to be essentially obligate pathogens. These strains have evolved a special ability to cause enteritis, enterocolitis, and colitis when ingested in sufficient quantities by a naïve host. At least five distinct pathotypes of intestinal pathogenic E. coli exist: (1) Shiga toxin–producing E. coli (STEC), which includes the subsets enterohemorrhagic E. coli (EHEC) and the recently evolved Shiga toxin–producing enteroaggregative E. coli (STEAEC); (2) enterotoxigenic E. coli (ETEC); (3) enteropathogenic E. coli (EPEC); (4) enteroinvasive E. coli (EIEC); and (5) enteroaggregative

E. coli (EAEC). Diffusely adherent E. coli (DAEC) and cytodetach ing E. coli are additional putative pathotypes. Lastly, a variant termed adherent invasive E. coli (AIEC) has been associated with Crohn disease (although a causal role remains unproven) but does not cause acute diarrheal disease. Contaminated food and water are the primary transmission vehicles for ETEC, STEC/EHEC/ST-EAEC, EIEC, and EAEC, whereas personto-person spread (direct or indirect) is the primary transmission route for EPEC and a secondary transmission route for STEC/EHEC/ ST-EAEC. Gastric acidity confers some protection against infection; therefore, persons with decreased stomach acid levels are especially susceptible. Humans are the major reservoir for such strains (except for STEC/EHEC, for which bovines are the main carriers); host range appears to be dictated by species-specific attachment factors. Although some overlap exists, each pathotype possesses a distinctive combina tion of virulence traits that results in a pathotype-specific pathogenic

mechanism (Table 166-3). With rare exceptions (e.g. DAEC), these strains are largely incapable of causing disease outside the intestinal tract. Whereas disease due to STEC/EHEC/ST-EAEC occurs primar ily in high-income countries, disease due to ETEC, EPEC, and EIEC occurs primarily in low- and middle-income countries in Asia, Africa, and Latin America, and disease due to EAEC occurs globally.

SHIGA TOXIN–PRODUCING E. COLI STEC/EHEC/ST-EAEC strains are pathogens that can cause hemorrhagic colitis and the hemolyticuremic syndrome (HUS). In contrast to other intestinal pathotypes, STEC/EHEC/ST-EAEC causes infections more frequently in highincome countries than in low and middle-income countries (LMICs). Several large outbreaks resulting from the consumption of fresh produce (e.g., lettuce, spinach, sprouts) and of undercooked ground beef have received significant media attention. In addition, a dramatic 2011 outbreak—mainly in Germany—involved an EAEC strain that acquired a Shiga toxin–encoding phage, resulting in a novel genotype, ST-EAEC

(O104:H4). This strain was transmitted to the primary cases by sprouted fenugreek seeds, with subsequent human-to-human trans mission, and resulted in >4000 cases and 54 deaths. STEC strains are the fourth most commonly reported cause of bac terial diarrhea in the United States (after Campylobacter, Salmonella, and Shigella). O157:H7 is the most prominent serotype among STEC strains, but many other serogroups have been described, including O6, O26, O45, O55, O91, O103, O111, O113, O121, and O145. Domesti cated ruminant animals, particularly cattle and young calves, serve as the major reservoir for STEC/EHEC. Ground or mechanically tender ized beef—the most common food source of STEC/EHEC strains—is often contaminated with intestinal bacteria from the source ani mals during processing. Furthermore, manure from cattle or other animals (including in the form of fertilizer) can contaminate produce (potatoes, lettuce, spinach, sprouts, fallen fruits, nuts, strawberries), and fecal runoff from manure can contaminate water systems. Dairy products and petting zoos are additional sources of infection. CHAPTER 166 Diseases Caused by Gram-Negative Enteric Bacilli

It is estimated that <102 colony-forming units (CFU) of STEC/ EHEC/ST-EAEC can cause disease. Therefore, not only can low levels of food or environmental contamination (e.g., in water swallowed while swimming) result in disease, but person-to-person transmission (e.g., at day-care centers and in institutions) is an important route for secondary spread. Laboratory-associated infections also occur. Illness due to this group of pathogens peaks in the summer months and occurs both as outbreaks and as sporadic cases. For STEC/EHEC/ST-EAEC, production of Shiga toxin (Stx2a–g and/or Stx1a,c,d) is a critical factor for occurrence of clinical dis ease, as demonstrated by the 2011 ST-EAEC outbreak. The stx gene is present on chromosomally integrated prophages, and various combinations of stx types and subtypes can occur in a given strain. Shigella dysenteriae strains that produce the closely related Shiga toxin Stx can also cause hemorrhagic colitis and HUS. Stx2 (especially Stx2a,c,d) appears to be more important than Stx1 in the development of HUS. All Shiga toxins studied to date are multimers; they comprise one A subunit that is enzymatically active and five identical B subunits that mediate binding to globosyl ceramides, which are membraneassociated glycolipids expressed on certain host cells. As in ricin, the Stx A subunit cleaves an adenine from the host cell's 28S rRNA, thereby irreversibly inhibiting ribosomal function (i.e., protein synthesis) and potentially leading to apoptosis. For full pathogenicity, STEC strains require additional properties such as acid tolerance and epithelial cell adherence. Most disease-caus ing isolates possess the chromosomal locus for enterocyte effacement (LEE). This pathogenicity island was first described in EPEC strains; it contains genes that mediate adherence to intestinal epithelial cells and a system that subverts host cells by the translocation of bacterial pro teins (type III secretion system). EHEC strains make up the subgroup of STEC strains that possess stx1 and/or stx2, as well as LEE. By con trast, the 2011 ST-EAEC outbreak strain lacked LEE yet was associated with a higher proportion of patients developing HUS (22%) than the historic average for STEC/EHEC outbreaks (2–8%). Data support the essential role of the 2011 outbreak strain's EAEC-associated virulence

factors (e.g., AAF/I fimbriae, serine proteases SigA, SepA) in adher ence, increased inflammation, and disruption of the intestinal epithe lial barrier, which in turn increased the systemic translocation of Stx2a.

After exposure to STEC/EHEC/ST-EAEC and a 3- to 4-day incuba tion period, colonization of the colon and perhaps the ileum results in symptoms. Colonic edema and an initial nonbloody secretory diarrhea may progress to the hallmark syndrome of grossly bloody diarrhea (iden tified

by history or examination). Significant abdominal pain and fecal leukocytes are common (70% of cases), whereas fever is not; absence of fever can incorrectly lead to consideration of noninfectious conditions (e.g., intussusception and inflammatory or ischemic bowel disease). Occasionally, infections caused by C. difficile, K. oxytoca (see “Klebsiella Infections,” below), Campylobacter, and Salmonella present in a similar fashion. STEC/EHEC disease is usually self-limited, lasting 5–10 days. A feared complication of infection with STEC/EHEC strains is HUS, which occurs 2–14 days after diarrhea, most often in young children (estimated to occur in 15% of infected children <10 years of age) or elderly patients. It is estimated that in the United States >50% of all HUS cases—and 90% of HUS cases in children, which is a leading cause of acute renal failure in this latter population—are caused by STEC/EHEC. By contrast, with ST-EAEC infection, HUS occurs more commonly among nonelderly adults, especially young women. HUS is mediated by the systemic translocation of Shiga toxins. Erythrocytes may serve as carriers of Stx to endothelial cells located in the small vessels of the kidney and brain. The subsequent development of throm botic microangiopathy (perhaps with direct toxin-mediated effects on various nonendothelial cells) commonly produces some combination of fever, hemolytic anemia (hematocrit <30%), thrombocytopenia (<150,000/mm3), renal failure, and encephalopathy. Stx-mediated complement activation also plays a role in the development of HUS. Although with dialysis support the mortality rate of HUS is <10%, sur vivors often have persisting renal and neurologic dysfunction. PART 5 Infectious Diseases ENTEROTOXIGENIC E. COLI ETEC is a major cause of endemic diar rhea in low- and middle-income countries and is responsible for an estimated 800 million cases annually. After weaning, children in these locales commonly experience several episodes of ETEC infection dur ing the first 3 years of life. The incidence of disease diminishes with age, a pattern that correlates with the development of mucosal immu nity to colonization factors (i.e., adhesins). In industrialized countries, ETEC is the most common agent of traveler’s diarrhea, causing 25–75% of cases. The incidence of infection may be decreased by prudent avoidance of potentially contaminated fluids and foods, particularly items that are raw, insufficiently cooked, peeled, or unrefrigerated (Chap. 130). ETEC infection is uncommon in the United States, but outbreaks secondary to consumption of food products imported from endemic areas have occurred. A large inoculum (106–108 CFU) is needed to produce disease, which usually develops after an incubation period of 12–72 h. After adherence of ETEC to enterocytes via colonization factors (e.g., CFA/I, CS), disease is mediated, primarily by a heat-labile toxin (LT) and/or a heat-stable toxin (ST), leading to diarrheal disease. Disease is less severe with strains that produce only LT. Both LT and ST cause net fluid secretion via activation of adenylate cyclase and/or guanylate cyclase C (ST) in the jejunum and ileum. The result is watery diarrhea accompanied by cramps. LT consists of an A and a pentameric B subunit and is structur ally and functionally similar to cholera toxin. Strong binding of the B subunit to the GM1 ganglioside on intestinal epithelial cells leads to the intracellular translocation of the A subunit, which functions as an ADP-ribosyltransferase. Mature ST is an 18- or 19-amino-acid secreted peptide that leads to increased intracellular concentrations of cGMP. Characteristically absent in ETEC-mediated disease are histopatho logic changes within the small bowel; mucus, blood, and inflammatory cells in stool; and fever. The disease spectrum of ETEC infection ranges from mild illness to a life-threatening, cholera-like syndrome. Although symptoms are usu ally self-limited (typically lasting for 3–5 days), infection may result in significant morbidity and mortality (>250,000 deaths annually, mostly

from profound volume depletion) when access to health care or suit able rehydration fluids is limited and when small and/or undernour ished children are affected. ENTEROPATHOGENIC E. COLI

EPEC causes disease primarily in young children, including neonates. The first E. coli pathotype recognized as an agent of diarrheal disease, EPEC was responsible for outbreaks of infantile diarrhea (including in hospital nurseries) in industrial ized countries in the 1940s and 1950s. At present, EPEC infection is uncommon in high-income countries, but among infants in low- and middle-income countries, it is an important cause of diarrhea (both sporadic and epidemic), often accompanied by vomiting and fever. Breast-feeding diminishes the incidence of EPEC infection. Rapid person-to-person spread may occur. Symptoms develop after colonization of the small bowel and a brief incubation period (1 or 2 days). Initial localized adherence to enterocytes via type IV bundle-forming pili leads to a charac teristic effacement of microvilli, with the formation of cuplike, actinrich pedestals mediated by factors in the LEE. Diarrhea production is a complex and regulated process in which host cell modulation by a type III secretion system plays an important role. Strains lacking bundleforming pili have been categorized as atypical EPEC (aEPEC); increas ing data support a role for these strains as intestinal pathogens in all age groups and among HIV-infected individuals. Diarrheal stool often contains mucus but not blood. Although EPEC diarrhea is usually selflimited (lasting 5–15 days), it may persist for weeks. ENTEROINVASIVE E. COLI EIEC, a relatively uncommon (or per haps underrecognized) cause of diarrhea, is rarely identified in the United States, although a few food-related outbreaks have been described. In low- and middle-income countries, sporadic disease is recognized infrequently in children and travelers. EIEC shares many genetic and clinical features, as well as a common ancestor, with Shigella. Both are intracellular pathogens for which viru lence is mediated by the presence of specific factors and by the loss or inactivation of other factors (antivirulence genes), which presumably occurred during these organisms' transition from an extracellular to an intracellular lifestyle. Colonization and invasion of the colonic mucosa, followed by replica tion therein and cell-to-cell spread (in part via a type III secretion sys tem), result in the development of inflammatory colitis. However, unlike Shigella, EIEC produces disease only with a large inoculum (108–1010 CFU) and is less virulent, typically causing only mild, self-limited (7–10 days), watery diarrhea. Onset generally follows an incubation period of 1–3 days. Occasionally, EIEC can cause a shigellosis-like (dysentery) syndrome characterized by fever, abdominal pain, tenesmus, and scant stool containing mucus, blood, and inflammatory cells. ENTEROAGGREGATIVE AND DIFFUSELY ADHERENT E. COLI EAEC has been described primarily in low- and middle-income countries and in young children. However, recent studies indicate that it may also be a relatively common cause of diarrhea in all age groups in industrialized countries. EAEC has been recognized increasingly as an important cause of traveler's diarrhea. It is highly adapted to humans—the prob able reservoir. A large inoculum is required for infection, which usually manifests as watery and sometimes persistent diarrhea in healthy but also malnourished or HIV-infected hosts. In vitro, EAEC cells exhibit a diffuse or "stacked-brick" pattern of adherence to small-intestine epithelial cells. Virulence factors that probably are necessary for disease are regulated in large part by the transcriptional activator AggR. The pathogenesis of EAEC disease begins with intestinal adherence, which results from stimulation of epithelial mucus production and bacterial biofilm formation, the latter mediated by fimbriae and possibly the mucinase Pic and dispersin. Inflammation ensues, resulting in epithelial cell exfoliation and intestinal secretion, which is mediated by the enterotoxins Pet, EAST-1, ShET1, and HlyE. An additional enteric pathotype, DAEC, is a heterogenous group associated with diarrheal disease, primarily in children 2–6 years of age in some LMICs, and may cause traveler's diarrhea. DAEC can also cause UTI. Diffuse adherence is observed on epithelial cells. The Afa/ Dr adhesins may contribute to the pathogenesis of such infections.

Diagnosis Acute infectious diarrhea can be classified as nonin flammatory or inflammatory; the latter is suggested by grossly bloody or mucoid stools or a positive test for fecal leukocytes, lactoferrin, or calprotectin (Chap. 138). ETEC, EPEC, DAEC, and EAEC cause non inflammatory diarrhea. Identification of these agents can be achieved with commercial multiplex molecular panels (e.g., the BioFire FilmArray Gastrointestinal Panel can detect STEC, ETEC, EPEC, EAEC, and EIEC). However, organism identification is rarely needed because the associated diseases are self-limited. ETEC causes the majority and EAEC a minority of cases of noninflammatory traveler's diarrhea; here again, however, definitive diagnosis generally is not necessary for man agement (as discussed below). If diarrhea persists for >10 days despite treatment, Giardia or Cryptosporidium (or, in immunocompromised hosts, certain opportunistic pathogens) should be sought. Because of the considerable public-health importance of STEC/ EHEC/ST-EAEC infections, including the threat of HUS, the CDC now recommends that all patients with community-acquired diarrhea, whether inflammatory or not, be evaluated for these pathogens by simultaneous culture (to provide an isolate for strain typing and for outbreak detection and control) and detection of Shiga toxin or the corresponding genes. The rationale for testing all cases of communityacquired diarrhea, regardless of clinical features, is that bloody stool and fecal white blood cells (or lactoferrin) are not reliably present with STEC/EHEC/ST-EAEC infection. In addition, the use of both tests increases diagnostic sensitivity over that with either test alone. O157 STEC/EHEC may be identified via culture by screening for E. coli strains that do not ferment sorbitol, with subsequent serotyp ing and testing for Shiga toxin. Selective or screening media are not available for culture-based detection of non-O157 STEC/EHEC/ ST-EAEC strains. Detection of Shiga toxins or toxin genes via DNAbased, enzyme-linked immunosorbent, and cytotoxicity assays offers the advantages of rapidity and detection of non-O157 STEC/EHEC/ ST-EAEC strains. Specimens positive for toxin but culture-negative for O157 should be forwarded to the local or state public-health laboratory for specialized testing. TREATMENT Intestinal E. coli Infections The mainstay of treatment for all diarrheal syndromes is replace ment of water and electrolytes. This measure is especially important for STEC/EHEC/ST-EAEC infection because appropriate volume expansion may protect against renal injury and improve outcome. The use of prophylactic antibiotics to prevent traveler's diarrhea generally should be discouraged, especially in light of high rates of antimicrobial resistance. However, in selected patients (e.g., those who cannot afford a brief illness or are predisposed to infection), the use of rifaximin, which is nonabsorbable and is well tolerated, is reasonable. When stools are free of mucus and blood, early patient-initiated treatment of traveler's diarrhea with a fluoroquinolone or azithro mycin decreases the duration of illness, and the use of loperamide may halt symptoms within a few hours. Although dysentery caused by EIEC is self-limited, antimicrobial therapy hastens the resolution of symptoms, particularly in severe cases. By contrast, antimicro bial therapy for STEC/EHEC/ST-EAEC infection (the presence of which is suggested by grossly bloody diarrhea without fever) should be avoided because antibiotics may increase the incidence of HUS (possibly via increased production/release of Stx). In the treatment of HUS, plasmapheresis is not recommended and the use of eculi zumab (inhibition of C5) should be limited to clinical trials. KLEBSIELLA INFECTIONS K. pneumoniae is the most important Klebsiella species from a medical standpoint, causing community-acquired, LTCF-acquired, and noso comial infections. K. oxytoca complex and K. (formerly Enterobacter) aerogenes are primarily pathogens in LTCFs and hospitals. Klebsiella

species are broadly prevalent in the environment and colonize the mucosal surfaces of mammals. In healthy humans, the prevalence of K. pneumoniae colonization is 5–35% in the colon and 1–5%

in the oropharynx; skin is usually colonized only transiently.

Most Klebsiella infections in Western countries are caused by “classic”

K. pneumoniae (cKp) and occur in hospitals and LTCFs. The most common clinical syndromes due to cKp are pneumonia, UTI, abdomi nal infection, intravascular device infection, surgical site infection, soft tissue infection, and secondary bacteremia. cKp strains have gained notoriety because of their propensity for acquiring treatmentconfounding antimicrobial resistance determinants and causing both localized and widespread outbreaks, such as with the global spread of cKp strains producing NDM-group MBLs. Clonal groups 11, 15, 101, 307, and 258, many members of which produce carbapenemases, are undergoing international dissemination. Transmission within or between institutions is common. K. pneumoniae is nearly fourfold more transmissible than E. coli, and, disconcertingly, carbapenemaseproducing strains are associated with increased spread compared with carbapenem-susceptible strains. In addition, hypervirulent K. pneumoniae (hvKp) strains that are phenotypically and clinically distinct from cKp have emerged recently, after their initial recognition in Taiwan in 1986. Although hvKp infections have occurred globally in all ethnic groups, most cases have been reported in individuals of Asian ethnicity residing in countries from the Asian Pacific Rim, but also in Asians living in other countries. Affected individuals often have diabetes mel litus. These demographics raise the possibility of a locale-specific distribution of the organism or an increased susceptibility of Asian hosts, especially those who are diabetic. In contrast to the usual health care–associated context for cKp infections in the West, hvKp can cause serious life- and organ-threatening infections in younger, healthy individuals from the community and can spread metastati cally from the primary site of infection or present with multiple sites of infection. Of concern, recent reports from Asian countries have demonstrated that hvKp is responsible for an increasing number of health care–associated or hospital-acquired infections. CHAPTER 166 Diseases Caused by Gram-Negative Enteric Bacilli
hvKp infection initially was characterized and distinguished from traditional infections caused by cKp strains by its (1) presenta tion as community-acquired monomicrobial pyogenic liver abscess

(Fig. 166-1, top), (2) occurrence in patients lacking a history of hepatobiliary disease, and (3) propensity for metastatic spread to distant sites. Subsequently, the hvKp pathotype has been recognized as the cause of extrahepatic abscesses and infections with or without liver involvement, including pneumonia; meningitis (in the absence of trauma or neurosurgery); endophthalmitis (Fig. 166-1, middle); splenic, psoas, prostatic, epidural, and brain abscesses; and necrotiz ing fasciitis. Survivors often suffer catastrophic morbidity, such as vision loss and major neurologic sequelae. Most recently, clinicians are faced with an even greater challenge—the confluence of antimi crobial resistance determinants such as carbapenemase and ESBL genes possessed by cKp and the virulence factors possessed by hvKp on the same or coexisting plasmids. The result is the evolution of MDR and XDR hvKp. K. pneumoniae subspecies rhinoscleromatis is the causative agent of rhinoscleroma, a granulomatous mucosal upper-respiratory infection that progresses slowly (over months or years) and causes necrosis and occasionally obstruction of the nasal passages. K. pneumoniae subspe cies ozaenae has been implicated as a cause of chronic atrophic rhinitis and rarely of invasive disease in compromised hosts. K. (Calymma tobacterium) granulomatis, a sexually transmitted pathogen, is the causative agent of granuloma inguinale (donovanosis) that results in chronic genital ulcers (Chap. 178). These Klebsiella pathotypes are usually isolated from patients in tropical climates and are genomically distinct from both cKp and hvKp. ■ ■INFECTIOUS

SYNDROMES Pneumonia Although cKp accounts for only a small proportion of cases of community-acquired pneumonia in Western countries

PART 5 Infectious Diseases FIGURE 166-1 Hypervirulent pathotype of K. pneumoniae (hvKp). Top: Abdominal CT scan of a previously healthy 24-year-old Vietnamese man shows a primary liver abscess (red arrow) with metastatic spread to the spleen (black arrow). (Courtesy of Drs. Chiu-Bin Hsaio and Diana Pomakova.) Middle: A previously healthy 33-yearold Chinese man presented with endophthalmitis. (AS Shon, RP Bajwa, TA Russo: Hypervirulent (hypermucoviscous) Klebsiella pneumoniae: A new and dangerous breed. Virulence 4:107, 2013.) Bottom: A hypermucoviscous phenotype (which does not necessarily equate with a mucoid phenotype) has been associated with hvKp strains. A positive string test is shown. However, this test is not optimally sensitive or specific. Identification of all 5 of the biomarkers iucA, iroB, peg-344, rmpA, and rmpA2 is presently the most accurate means to identify hvKp.

(Chap. 131), cKp and K. oxytoca are common causes of pneumonia among LTCF residents and hospitalized patients because of increased rates of oropharyngeal colonization with these organisms in such indi viduals. Mechanical ventilation is an important risk factor. In Asia and South Africa, community-acquired pneumonia due to hvKp is becom ing increasingly common, rivaling Streptococcus pneumoniae, and may occur in younger patients with no underlying disease. Klebsiella is also a common cause of pneumonia in severely malnourished children in LMICs. As in all pneumonias due to enteric GNB, typical manifestations include production of purulent sputum and evidence of airspace dis ease. Presentation with earlier, less extensive infection is now more common than is the classically described lobar infiltrate, bulging fis sure, and currant-jelly sputum. Pulmonary infection due to hvKp that has spread metastatically (e.g., from a hepatic abscess) usually includes nodular bilateral densities, more commonly in the lower lobes. Pulmo nary necrosis, pleural effusion, and empyema can occur with disease progression. UTI cKp accounts for only 1–2% of UTI episodes among other wise healthy adults but for 5–17% of episodes of UTI in patients with anatomic and functional abnormalities of the urinary tract, including indwelling urinary catheter use (complicated UTI). UTI due to hvKp presents more commonly as renal or prostatic abscess due to bac teremic spread than as ascending infection from the urethra and bladder. Abdominal Infection cKp causes a spectrum of abdominal infec tions similar to that caused by E. coli but is less frequently isolated than E. coli. hvKp is a common cause of monomicrobial communityacquired pyogenic liver abscess; in the Asian Pacific Rim, it has been recovered with steadily increasing frequency over the past two decades, replacing E. coli as the most common pathogen causing this syndrome. hvKp also is increasingly described as a cause of spontaneous bacterial peritonitis and splenic abscess. Other Infections When cKp and K. oxytoca cause cellulitis or soft tissue infection, the process most frequently involves devitalized tissue (e.g., decubitus and diabetic ulcers, burn wounds) and immunocom promised hosts. cKp and K. oxytoca cause some cases of surgical site infection and nosocomial sinusitis as well as occasional cases of osteo myelitis contiguous to soft tissue infection, nontropical myositis, and meningitis (during the neonatal period and after neurosurgery). By contrast, hvKp has become an important cause of community-acquired monomicrobial necrotizing fasciitis, meningitis, endophthalmitis (Fig. 166-1, middle), and abscesses within the brain, subdural space, and epidural space, particularly in the Asian Pacific Rim but also glob ally. Cytotoxin-producing strains of K. oxytoca have been implicated as a cause of non–C. difficile antibiotic-associated hemorrhagic colitis. Bacteremia Klebsiella infection at any site can produce bactere mia. Infections of the urinary tract, respiratory tract, and

abdomen (especially hepatic abscess) each account for 15–30% as the source of Klebsiella bacteremia. Intravascular device–related infections account for another 5–15% of episodes, and surgical site and miscellaneous infections account for the rest. Klebsiella is an occasional cause of sepsis in neonates and of bacteremia in neutropenic patients. However, like other enteric GNB, Klebsiella rarely causes endocarditis or other endovascular infections, although endocarditis can involve extensive valvular destruction when it occurs. ■ ■DIAGNOSIS Klebsiellae are readily isolated and identified in the laboratory. These organisms usually ferment lactose, although the subspecies rhinoscle romatis and ozaenae are nonfermenters and are indole-negative. hvKp frequently possesses a hypermucoviscous phenotype (Fig. 166-1, bottom), although the sensitivity and specificity of the string test are less than optimal. Identification of all 5 of the biomarkers iucA, iroB, peg-344, rmpA, and rmpA2 is presently the most accurate means to identify hvKp in both antimicrobial sensitive and MDR isolates, although cur rently, this test is not routinely available.

TREATMENT Klebsiella Infections K. (formerly Enterobacter) aerogenes has a similar resistance profile to E. cloacae, the treatment of which is discussed below. K. pneu moniae and K. oxytoca have similar antibiotic resistance profiles; both are intrinsically resistant to ampicillin. The prevalence of acquired resistance in K. pneumoniae and K. oxytoca is generally

> 30% for amoxicillin-clavulanate, ampicillin-sulbactam, nitrofu rantoin, and TMP-SMX and ~10−20% for fluoroquinolones, piper acillin-tazobactam, fosfomycin, and omadacycline. USNHSN data from 2015−2017 identified 25% of K. pneumoniae as ESBL-producing strains; higher rates are reported from Asia, South America, and Africa. Although prevalence of ESBL-producing strains is greatest in LTCF, isolates of cKp that produce CTX-M ESBLs are increasingly described from the community. Oral treat ment for infection due to ESBL-producing strains is more challeng ing with Klebsiella than with E. coli because of the comparatively poor activity of nitrofurantoin, the lesser activity of fosfomycin (~80%), and limited available data regarding pivmecillinam (>80%) and omadacycline (75–100% susceptible for ESBL-producing iso lates, but 60% if resistant to tetracycline). Predictably, the ESBL-driven use of carbapenems has selected for strains of cKp and K. oxytoca that produce carbapenemases (8–18% based on the study and locale, 8.6% prevalence from 2015−2017 USNHSN data). Treatment can be problematic for such organisms, especially those producing MBLs (e.g., NDM), for which the high est prevalences are in cKp and K. oxytoca isolates from Eastern Europe and Asia and among health care–associated isolates. Likewise, hvKp strains from Asia are also increasingly reported to produce ESBLs and carbapenemases. Treatment options for carbapenem-resistant Klebsiella are similar to those described for E. coli and depend on the class of carbapen emase produced (see “Carbapenemase,” above); consultation with infectious disease experts is advised. For carbapenem-susceptible strains, the most predictably active agents include carbapenems, amikacin, ceftazidime-avibactam, ceftolozane-tazobactam, poly myxins, cefiderocol, tigecycline, eravacycline, and omadacycline. Empirical treatment decisions for the critically ill patient should be dictated by local susceptibility

> patterns, patient-specific risk factors, and the site of infection. PROTEUS INFECTIONS Proteus species are part of the colonic flora of a wide variety of mam mals, birds, fish, and reptiles. The ability of these GNB to generate histamine from contaminated fish has implicated them in the patho genesis of scombroid (fish) poisoning (Chap. 471). P. mirabilis causes 90% of Proteus infections, which occur in the community, LTCFs, and hospitals. By contrast, Proteus vulgaris and Proteus penneri are associated primarily with infections acquired in LTCFs or hospitals. Correspondingly, P. mirabilis colonizes healthy humans (up to 50%), whereas P. vulgaris and P. penneri are isolated primarily from individuals with underlying disease. By far the most common site of Proteus infection is the urinary tract, where the prin cipal known urovirulence factors of Proteus include adhesins, flagella, IgA-IgG protease, iron acquisition systems, and urease. Proteus less commonly causes infection at a variety of other extraintestinal sites. ■ ■INFECTIOUS SYNDROMES UTI P. mirabilis causes only 1–2% of UTIs in healthy women, and Proteus species collectively cause only 5% of hospital-acquired UTIs. However, Proteus is responsible for 10–15% of cases of complicated UTI, primarily those associated with catheterization; indeed, Proteus accounts for 20–45% of urine isolates from chronically catheterized patients. This high prevalence is due in part to bacterial production of urease, which hydrolyzes urea to ammonia and results in alkaliza tion of the urine. In alkaline urine, organic and inorganic compounds

precipitate, contributing to the formation of struvite and carbonate– apatite crystals, biofilms on catheters, and/or frank calculi. Proteus becomes associated with the stones and biofilms; thereafter, it usually cannot be eradicated without removal of the stones or catheter. Over time, staghorn calculi may form within the renal pelvis and lead to obstruction and renal failure. Although biologically plausible, clinical support is lacking for the concept that urine samples exhibiting unex plained alkalinity should be cultured, and that isolation of a Proteus species (or other urea-splitting organism) should prompt consideration of an evaluation for urolithiasis.

Other Infections Proteus occasionally causes pneumonia (primar ily in LTCF residents or hospitalized patients), nosocomial sinusitis, intraabdominal abscesses, biliary tract infection, surgical site infec tion, soft tissue infection (especially decubitus and diabetic ulcers), and osteomyelitis (primarily contiguous); in rare cases, it causes non tropical myositis. In addition, Proteus uncommonly causes neonatal meningitis, with the umbilicus frequently implicated as the source; this disease is often complicated by development of a cerebral abscess. Otogenic brain abscess also occurs. Bacteremia Most episodes of Proteus bacteremia originate from the urinary tract, although intravascular devices and any of the less com mon sites of Proteus infection also are potential sources. Endovascular infection is rare. Proteus species are occasional agents of sepsis in neo nates and of bacteremia in neutropenic patients. ■ ■DIAGNOSIS Proteus is readily isolated and identified in the laboratory. Most strains are lactose-negative, produce H_2S, and demonstrate characteristic swarming motility and distinct odor on agar plates. P. mirabilis and

P. penneri are indole-negative, whereas P. vulgaris is indole-positive. The inability to produce ornithine decarboxylase differentiates P. penneri from P. mirabilis. CHAPTER 166 Diseases Caused

by Gram-Negative Enteric Bacilli
TREATMENT Proteus Infections Intrinsic resistance occurs in all Proteus spp. to nitrofurantoin, polymyxins, imipenem, and the tetracycline derivatives (e.g., tige cycline, eravacycline, omadacycline) and, in P. vulgaris and P. penneri, also to ampicillin and the first- and second-generation cephalosporins. Acquired resistance (% of isolates) occurs in P. mirabilis to ampicillin (15–65%), and in Proteus spp. to fluoroqui nolones (10–55%), fosfomycin (7–22%), and TMP-SMX (20–50%). In P. mirabilis, ampicillin-sulbactam is more active than ampicillin, with resistance rates of 6–18%, but the prevalence of ESBL produc tion (which confers ampicillin-sulbactam resistance) is increasing in the United States (5–10%) and Asia (up to 60%). Isolates of P. mirabilis that produce CTX-M ESBLs have been recovered from ambulatory patients with no recent health care contact (see the sec tion on the treatment of extraintestinal E. coli infections for treat ment considerations). Acquired carbapenem resistance remains relatively infrequent (<10%). However, production of MBLs (e.g., NDM) limits treatment options due to the inherent resistance of Proteus spp. to polymyxins and tetracycline derivatives (see “Carbapenemase,” above). For critically ill patients, agents with excellent activity overall against Proteus spp. (90–100% of isolates susceptible) include carbapenems (excepting imipenem), amikacin, piperacillin-tazobactam, aztreonam, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam. ENTEROBACTER AND CRONOBACTER INFECTIONS The E. cloacae complex is responsible for most Enterobacter infections, whereas Cronobacter sakazakii (formerly Enterobacter sakazakii), Crono bacter malonaticus, E. cancerogenus, E. asburiae, E. hormaechei, E. kobei, E. ludwigii, and E. gergoviae are less commonly isolated (<1% for each). Enterobacter bugandensis has been recently described as an agent of

sepsis in neonates and was isolated from the International Space Station. Enterobacter spp. cause primarily health care–related infections. The organisms are widely prevalent in foods, environmental sources (includ ing equipment at health care facilities), and a variety of animals.

Colonization with these organisms is uncommon among healthy humans but increases significantly with LTCF residence or hospitaliza tion. Although colonization is an important prelude to infection, direct introduction via IV lines (e.g., contaminated IV fluids or pressure monitors) or contaminated non-FDA-approved stem cell products also occurs. Extensive antibiotic resistance has developed in Enterobacter spp. and probably has contributed to these organisms’ emergence as prominent nosocomial pathogens. Risk factors for Enterobacter infec tion include prior antibiotic treatment, comorbid disease, and ICU residency. Enterobacter spp. causes a spectrum of extraintestinal infec tions similar to those described for other GNB. ■ ■INFECTIOUS SYNDROMES The most commonly encountered syndromes include pneumonia, UTI (particularly catheter-associated), intravascular device–related infection, surgical site infection, and abdominal infection (primarily postoperative or related to devices such as biliary stents). Nosocomial sinusitis, men ingitis related to neurosurgical procedures (including use of intracranial pressure monitors), osteomyelitis, and endophthalmitis after eye surgery are less frequent. Neonates (particularly if low-birth-weight) are at risk for C. sakazakii infection, including neonatal bacteremia, necrotiz ing enterocolitis, and meningitis (which is often complicated by brain abscess or ventriculitis). Contaminated powdered infant formula has been implicated as a source for such neonatal infections. The WHO recommends that, to reduce the initial number of bacteria, powdered infant formula should be reconstituted with hot water (>70°C) and, to limit replication of residual bacteria, the reconstituted formula should be stored at <5°C or its storage time minimized. PART 5 Infectious Diseases Enterobacter bacteremia can result

from primary infection at any anatomic site. In bacteremia of unclear origin, particularly in an out break setting, sources for consideration should include contaminated IV fluids or medications, blood components or plasma derivatives, catheter-flushing fluids, pressure monitors, and dialysis equipment. Enterobacter can also cause bacteremia in neutropenic patients. Entero bacter endocarditis is rare, occurring primarily in association with IV drug use or prosthetic valves. ■ ■DIAGNOSIS Enterobacter is readily isolated and identified in the laboratory. Most strains are lactose-positive and indole-negative. TREATMENT Enterobacter Infections E. cloacae is intrinsically resistant to ampicillin, ampicillin-sulbac tam, ampicillin-clavulanate, the first-generation cephalosporins, and the cephamycins. The prevalence of acquired resistance has ranged from 15 to 40% for piperacillin-tazobactam, 5 to 23% for polymyxins, 15 to 17% for fosfomycin, 15 to 30% for TMP-SMX, and 5 to 20% for fluoroquinolones and is ~10% for omadacycline (53% if tetracycline resistant). USNHSN data from 2015−2017 identified at least 9% of E. cloacae isolates as presumptively ESBLproducing, based on cefepime resistance. The prevalence of ESBLs in E. cloacae outside of the United States is 20−50%. The use of third-generation cephalosporins can induce or select for stable derepression of AmpC β-lactamase. Because resistance may emerge during therapy (in one study, this phenomenon was documented in 20% of clinical isolates), these agents should be avoided in the treatment of severe Enterobacter infection. Cefepime is stable to hydrolysis by AmpC β-lactamases; thus, it is a suitable option for treatment of Enterobacter infections so long as ESBL is not co-produced. Overall, resistance prevalence generally ranges from 10 to 25% for cefepime and 25 to 50% for aztreonam and the third-generation cephalosporins. Carbapenem resistance remains relatively uncommon (USNHSN data from 2015−2017 identified a

5% prevalence) and is more commonly associated with a combina tion of increased AmpC expression and decreased permeability due to porin mutations rather than carbapenemase production, although acquisition of carbapenemase genes is increasing (see “Carbapen emase,” above). Uncertainty exists on the optimal treatment for non-CP-CR-Enterobacter spp. Fortunately, overall, the percentage of susceptibility is high (90–99%) for carbapenems, amikacin, ceftazi dime-avibactam, cefiderocol, tigecycline, eravacycline, and omada cycline (the latter three for tetracycline-susceptible isolates). Once susceptibility data for a patient’s isolate become available, de-escalation of the antimicrobial regimen is advisable whenever possible. SERRATIA INFECTIONS S. marcescens causes >90%, and Serratia liquefaciens complex <10%, of Serratia infections. Serratiae are found primarily in the environment (including in health care institutions), particularly in moist settings. Serratiae have been isolated from a variety of animals, insects, and plants, but only infrequently from healthy humans. In LTCFs and hospitals, reservoirs for the organisms include the hands and finger nails of health care personnel, food, milk (on neonatal units), sinks, medical equipment or devices, IV solutions or parenteral medications (particularly those generated by compounding pharmacies), prefilled syringes and multiple-access medication vials (e.g., for heparin, pro pofol, saline), blood products (e.g., platelets), hand soaps and lotions, irrigation solutions, and even disinfectants such as chlorhexidine. Infection results from either direct inoculation (e.g., via con taminated injected substances [IV fluids, medications, or recreational drugs] or snake bite) or colonization (primarily of the respiratory tract). Sporadic infection is most common, but outbreaks (often involving MDR strains in adult and neonatal ICUs) also occur. Hygiene, medication-compounding standards, sterile technique, and infection control programs are critical measures to prevent infection. The spectrum of extraintestinal infections caused by Serratia is similar to that for other GNB. Serratia species are usually considered to cause mainly health care–associated infections; they account for 1–3% of hospital-acquired infections. However,

population-based laboratory surveillance studies in Canada and Australia have demonstrated that community-acquired Serratia infections occur more commonly than was previously appreciated, and case reports have documented serious infection in otherwise healthy hosts. Serratia also is one of the patho gens associated with chronic granulomatous disease. ■ ■INFECTIOUS SYNDROMES The most common primary sites of Serratia infection are the respira tory and genitourinary tracts, intravascular devices, the eye (contact lens–associated keratitis and other ocular infections), surgical wounds, and the bloodstream (from contaminated infusions), although most episodes of Serratia bacteremia arise from one of the listed focal infec tions rather than contaminated infusate. Less common syndromes are soft tissue infections (including myositis, fasciitis, mastitis), osteomy elitis, abdominal and biliary tract infections (usually postprocedural), and septic arthritis (primarily from intraarticular injections). Serratiae are uncommon causes of neonatal meningitis; postsurgical meningitis, endophthalmitis, or breast implant infection; and bacteremia in neu tropenic patients. Endocarditis is rare, occurring most commonly in IV drug users. ■ ■DIAGNOSIS Serratiae are readily cultured and identified by the laboratory and are usually lactose- and indole-negative. The red pigmentation of some

S. marcescens strains and Serratia rubidaea can produce distinctive clin ical findings (e.g., pink breast milk or hypopyon; pseudohemoptysis). TREATMENT Serratia Infections Most Serratia strains (>80%) are intrinsically resistant to ampi cillin, amoxicillin-clavulanate, ampicillin-sulbactam, first- and

second-generation cephalosporins, cephamycins, nitrofurantoin, and polymyxins; likewise, tetracycline derivatives are poorly active. By contrast, fluoroquinolones, TMP-SMX, piperacillin-tazobactam, fosfomycin, and omadacycline are active against 85−95% of U.S. and European isolates, including those resistant to tetracycline. Both in the United States and globally, the prevalence of ESBLproducing isolates is generally low (<10%), but rates of 20–30% have been reported in Asia and Latin America. Induction or selec tion of variants with stable de-repression of chromosomal AmpC β-lactamases during therapy with third-generation cephalosporins is considered to be uncommon. Resistance prevalence generally ranges from 10 to 20% for aztreonam and the third-generation cephalosporins. Acquisition of carbapenemase-encoding genes is uncommon but increasing. Production of MBL (e.g., NDM) limits treatment options due to Serratia's predictable resistance to poly myxins and tetracycline derivatives (see "Carbapenemase," above). For critically ill patients, the most active agents overall (>90% susceptible) are carbapenems, piperacillin-tazobactam, cefepime, amikacin, ceftazidime-avibactam, and ceftolozane-tazobactam. CITROBACTER INFECTIONS C. freundii and Citrobacter koseri cause most human Citrobacter infec tions, which are epidemiologically and clinically similar to Entero bacter infections. Citrobacter species are commonly present in water, food, soil, and certain animals. Colonization with these organisms is uncommon among healthy humans but increases significantly with LTCF residence or hospitalization. Citrobacter species account for 1–2% of nosocomial infections. The affected hosts are usually immu nocompromised and/or have comorbid disease or disruption of skin or mucosal barriers. Infection from treatment with contaminated, non-FDA-approved stem cell products has been described. Citrobacter causes extraintestinal infections like those described for other GNB. ■ ■INFECTIOUS SYNDROMES The urinary tract accounts for 40–50% of Citrobacter infections. Less commonly involved sites include the biliary tree (particularly with stones or obstruction), the respiratory tract, surgical sites, soft tissue (e.g., decubitus ulcers), the peritoneum, and intravascular devices. Osteomyelitis (usually

from a contiguous focus), central nervous sys tem infection in adults (from neurosurgical or other types of meningeal disruption), and myositis occur rarely. Citrobacter (primarily C. koseri) also causes 1–2% of neonatal meningitis cases, of which 50–80% are complicated by brain abscess. Further, case reports in adults suggest that C. koseri infection has a predilection for abscess formation. Citro bacter bacteremia is most often due to UTI, biliary/abdominal infec tion, or intravascular device infection, and occurs in some neutropenic patients. Endocarditis and other endovascular infections are rare. ■ ■DIAGNOSIS Citrobacter species are readily isolated and identified; 35–50% of iso lates are lactose-positive, and 100% are oxidase-negative. C. freundii is indole-negative, whereas C. koseri is indole-positive. TREATMENT Citrobacter Infections C. freundii is more antibiotic-resistant than is C. koseri. Most C. freundii isolates are intrinsically resistant to ampicillin, ampicillinsulbactam, amoxicillin-clavulanate, first-generation cephalospo rins, and cephamycins. C. koseri exhibits intrinsic resistance to ampicillin and ampicillin-sulbactam. Overall, the prevalence of acquired resistance generally ranges from 15 to 35% for third-gen eration cephalosporins, piperacillin-tazobactam, fluoroquinolones, and TMP-SMX and is ~10% for nitrofurantoin and omadacycline (but 39% for omadacycline if tetracycline-resistant). The prevalence of ESBL production ranges from 5 to 30%. The use of third-generation cephalosporins may result in the induction or selection of variants with stable de-repression of chromosomal AmpC β-lactamases

during therapy. Presently, <10% of isolates have acquired car bapenemases (see “Carbapenemase,” above). Carbapenems, ami kacin, fosfomycin, polymyxins, cefepime, ceftolozane-tazobactam, ceftazidime-avibactam, cefiderocol, tigecycline, eravacycline, and omadacycline (the latter three if tetracycline-susceptible) are the most active agents against Citrobacter isolates (>90% susceptible).

MORGANELLA AND PROVIDENCIA INFECTIONS M. morganii, Providencia stuartii, and (less frequently) Providencia rettgeri are the members of their respective genera that cause systemic human infections. P. alcalifaciens has been implicated as a cause of food-borne gastroenteritis. These organisms’ epidemiologic asso ciations, pathogenic properties, and clinical manifestations resemble those of Proteus species. Morganella and Providencia occur more commonly among LTCF residents than among hospitalized patients, largely resulting from chronic urinary catheter use. Because of these organisms’ intrinsic resistance to polymyxins and tigecycline, they may become more common in settings with extensive use of these agents. ■ ■INFECTIOUS SYNDROMES These species are primarily urinary tract pathogens, causing UTIs that are most often associated with long-term (>30-day) catheterization. Such infections commonly lead to biofilm formation and catheter encrustation (sometimes causing catheter obstruction) or the devel opment of struvite bladder or renal stones (sometimes causing renal obstruction, abscess, and extrarenal extension, and serving as foci for relapse). They can cause purple urine (“purple bag syndrome”), as can P. mirabilis, K. pneumoniae, E. coli, and P. aeruginosa. Morganella is also commonly isolated from snakebite infection. CHAPTER 166 Other, less common infectious syndromes due to Morganella and Providencia include surgical site infection, soft tissue infection (pri marily involving decubitus and diabetic ulcers), burn site infection, pneumonia (particularly ventilator-associated), intravascular device infection, and intraabdominal infection. Rarely, the other extraintesti nal infections described for GNB also occur. Bacteremia is uncommon; when it does occur, any infected site can serve as the source, but the urinary tract accounts for most cases, followed by surgical site, soft tis sue, and hepatobiliary infections. Diseases Caused by Gram-Negative Enteric Bacilli ■ ■DIAGNOSIS M. morganii and Providencia are readily isolated and identified. Nearly all isolates

are lactose-negative and indole-positive. TREATMENT Morganella and Providencia Infections Morganella and Providencia are intrinsically resistant to ampicil lin, ampicillin-clavulanate, ampicillin-sulbactam, first-generation cephalosporins, nitrofurantoin, tetracyclines and derivatives (e.g., tigecycline), imipenem (but not the other carbapenems), and the polymyxins. P. stuartii additionally exhibits intrinsic resistance to gentamicin and tobramycin, as does M. morganii to second-generation cephalosporins. Fosfomycin is poorly active (>50% resistance). The prevalence of resistance generally ranges from 10 to 30% for the third-generation cephalosporins, from 10 to 40% for fluoroquino lones, and from 20 to 40% for TMP-SMX; the prevalence is more widely variable for piperacillin-tazobactam. The prevalence of ESBL production is generally <10%. The prevalence of acquired car bapenemase production is <10%. Production of MBL (e.g., NDM) limits treatment options due to the inherent resistance of Proteeae to polymyxins and tetracycline derivatives (see “Carbapenemase,” above). Overall, the most active agents (>90% of isolates suscep tible) are carbapenems (excepting imipenem), amikacin, cefepime, ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol. Removal of a colonized urinary catheter or stone is critical for eradication of UTI.

Revision #1
Created 2026-01-06 16:33:09 UTC by Omar Ayman
Updated 2026-01-06 16:33:09 UTC by Omar Ayman