E. coli can cause either intestinal or extraintestinal infection, depending on the particular pathotype, and *Edwardsiella tarda* can cause both intestinal and extraintestinal infection. *Klebsiella* primarily causes extraintestinal infection, but hemorrhagic colitis has been associated with a toxin-producing variant of *Klebsiella oxytoca*. Depending on both the host and the pathogen, nearly every organ or body cavity can be infected with GNB. *E. coli* and—to a lesser degree—*Klebsiella* account for most extraintestinal infections due to GNB and are the most virulent pathogens within this group; this virulence is demonstrated by the ability of *E. coli* and *Klebsiella pneumoniae* (primarily the hypervirulent variant) to cause severe infections in healthy, ambulatory hosts from the community. However, the other genera are also important, 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 the severity of illness. Especially problematic are pneumonia and bacteremia (arising from any source), particularly when complicated by organ failure (severe sepsis) and/or shock, for which the associated mortality rates are 20–50%.

DIAGNOSIS

Isolation of GNB from sterile sites almost always implies infection, whereas their isolation from nonsterile sites, particularly from open soft-tissue wounds and the respiratory tract, requires clinical correlation to differentiate colonization from infection. Tentative laboratory identification based on lactose fermentation and indole production (described for each genus below), which usually is possible before final identification of the organism and determination of its antimicrobial susceptibilities, may help to guide empirical antimicrobial therapy.

TREATMENT INFECTIONS CAUSED BY GRAM-NEGATIVE ENTERIC BACILLI

(See also Chap. 170) Evidence indicates that initiation of appropriate empirical antimicrobial therapy early in the course of GNB infections (particularly serious infections) leads to improved outcomes. The ever-increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB; the lag between published (historical) and current resistance rates; and variations by species, geographic location, regional antimicrobial use, and hospital site (e.g., intensive care units [ICUs] versus wards) necessitate familiarity with evolving patterns of antimicrobial resistance for the selection of appropriate empirical therapy. Factors predictive of isolate resistance include recent antimicrobial use, a health care association (e.g., recent or ongoing hospitalization, dialysis, residence in an LTCF), or international travel (e.g., to Asia, Latin America, Africa, southern Europe). For appropriately selected patients, it may be prudent initially, while susceptibility results are awaited, to use two potentially active agents with the rationale that at least one agent will be active. If broad-spectrum treatment has been initiated, it is critical to switch to the most appropriate narrower-spectrum agent when information on antimicrobial susceptibility becomes available. Such responsible antimicrobial stewardship will slow down the ever-escalating cycle of selection for increasingly resistant bacteria, decrease the likelihood of *Clostridium 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). At present, the most reliably active agents against enteric GNB are the carbapenems (e.g., imipenem), the aminoglycoside amikacin, the fourth-generation cephalosporin cefepime, the β-lactam/β-lactamase inhibitor combination piperacillin-tazobactam, and the polymyxins (e.g., colistin or polymyxin B). The number of antimicrobials effective against certain Enterobacteriaceae is shrinking. Truly pan-resistant GNB exist, and it is unlikely that new agents will come to market in the short term. Accordingly, the presently available antimicrobials must be used judiciously.

β-Lactamases, which inactivate β-lactam agents, are the most important mediators of resistance to these drugs in GNB. Decreased permeability and/or active efflux of β-lactam agents, although less common, may occur alone or in combination with β-lactamase-mediated resistance.

Broad-spectrum β-lactamases (e.g., TEM, SHV), which mediate resistance to many penicillins and first-generation cephalosporins, are frequently expressed in enteric GNB. These enzymes are inhibited by β-lactamase inhibitors (e.g., clavulanate, sulbactam, tazobactam). They usually do not hydrolyze third- and fourth-generation cephalosporins or cephamycins (e.g., cefoxitin).

Extended-spectrum β-lactamases (ESBLs; e.g., CTX-M, SHV, TEM) are modified broad-spectrum enzymes that confer resistance to the same drugs as well as to third-generation cephalosporins, aztreonam, and (in some instances) fourth-generation cephalosporins. GNB that express ESBLs may also possess porin mutations that result in decreased uptake of cephalosporins and β-lactam/β-lactamase inhibitor combinations. The prevalence of acquired ESBL production, particularly of CTX-M-type enzymes, is increasing in GNB worldwide, in large part due to the presence of the responsible genes on large transferable plasmids with linked or associated resistance to fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, and tetracyclines. To date, ESBLs are most prevalent in *K. pneumoniae*, *K. oxytoca*, and *E. coli* but also occur (and are probably underrecognized) in *Enterobacter*, *Citrobacter*, *Proteus*, *Serratia*, and other enteric GNB. At present, the rough regional prevalence of ESBL-producing GNB is India > China > rest of Asia, Latin America, Africa, southern Europe > northern Europe > United States, Canada, and Australia. International travel to high-prevalence regions increases the likelihood of colonization with these strains. ESBL-producing GNB were initially described in hospitals (ICUs > wards) and LTCFs, where outbreaks occurred in association with extensive use of third-generation cephalosporins. However, over the last decade, the incidence of uncomplicated cystitis due to CTX-M ESBL-containing *E. coli* has increased worldwide (including in the United States) among healthy ambulatory women without health care or antimicrobial exposure. Antimicrobial use in food animals has also been implicated in the rise of ESBLs.

The carbapenems are the most reliably active β-lactam agents against ESBL-expressing strains. Clinical experience with alternatives is more limited, but, for organisms susceptible to piperacillin-tazobactam (minimal inhibitory concentration [MIC], ≤4 μg/mL), this agent—at a dosage of 4.5 g q6h—may offer a carbapenem-sparing alternative, at least for *E. coli*. The role of tigecycline is unclear despite its excellent in vitro activity; *Proteus*, *Morganella*, and *Providencia* are inherently resistant, and attainable serum and urine levels are low. Therefore, caution appears to be prudent, especially with serious infections, until more clinical data become available. Oral options for the treatment of strains expressing CTX-M ESBLs are limited, with fosfomycin being the most reliably active agent (see section below on the treatment of extraintestinal *E. coli* infections).

AmpC β-lactamases, when induced or stably derepressed to high levels of expression, confer resistance to the same substrates as ESBLs plus the cephamycins (e.g., cefoxitin and cefotetan). The genes encoding these enzymes are primarily chromosomally located and therefore may not exhibit the linked or associated resistance to fluoroquinolones, TMP-SMX, aminoglycosides, and tetracyclines that is common with ESBLs. These enzymes are problematic for the clinician: resistance may develop during therapy with third-generation cephalosporins, resulting in clinical failure, particularly in the setting of bacteremia. Although chromosomal AmpC β-lactamases are present in nearly all members of the Enterobacteriaceae family, the risk of clinically significant induction of high expression levels or selection of stably derepressed mutants with cephalosporin treatment is greatest with *Enterobacter cloacae* and *Enterobacter aerogenes*, lower with *Serratia marcescens* and *Citrobacter freundii*, and lowest with *Providencia* and *Morganella morganii*. In addition, rare