strains of *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae have acquired plasmids containing inducible AmpC β-lactamase genes. Carbapenems are a viable treatment option. The fourth-generation cephalosporin cefepime may be an appropriate option if the concomitant presence of an ESBL can be excluded and source control is achieved. Other carbapenem-sparing alternatives to consider if isolates are susceptible in vitro are fluoroquinolones, piperacillin-tazobactam, TMP-SMX, tigecycline, and aminoglycosides, although clinical data are limited.

Carbapenemases (e.g., KPC [class A]; NDM-1, VIM, and IMP [class B]; and OXA-48 [class D]) confer resistance to the same drugs as ESBLs and also to cephamycins and carbapenems. Similar to ESBLs, carbapenemases are usually encoded on large transferable plasmids, which often encode linked resistance to fluoroquinolones, TMP-SMX, tetracyclines, and aminoglycosides. Unfortunately, carbapenemase-producing Enterobacteriaceae are becoming increasingly common, particularly in Asia, and infection with these strains is associated with elevated mortality rates. This reality has prompted the Centers for Disease Control and Prevention (CDC) to categorize carbapenem-resistant Enterobacteriaceae as an "urgent threat" to health care. Carbapenemase production by Enterobacteriaceae is most prevalent in *K. pneumoniae* and *E. coli* but has been described in nearly all members of the family. Automated susceptibility systems may be unreliable for detection of carbapenemases. An elevated MIC or a diminished zone diameter for meropenem or imipenem should prompt genotypic confirmation, if available. Alternatively, the phenotype can be confirmed with a modified Hodge test (which detects classes A, B, and D, although results can be false positive) and/or inhibition tests with boronic acid (class A), EDTA (class B), or dipicolinic acid (class B). Carbapenem resistance may also occur in the absence of carbapenemase production and can be mediated by AmpC β-lactamase and ESBL production coupled with modifications in permeability/efflux.

For treatment of carbapenem-resistant Enterobacteriaceae, tigecycline and colistin are the parenteral agents with the most reliable in vitro activity. However, because tigecycline reaches only low serum and urine concentrations, caution is warranted in using it to treat bacteremia and perhaps urinary tract infection (UTI), although a few case reports describe some success with tigecycline therapy for UTI. Colistin has nephrotoxic and neurotoxic potential. Furthermore, increasing resistance has been described to both of these agents. Thus the clinician is left with few or no therapeutic options. Aminoglycosides may have some utility if active. Fosfomycin is often active in vitro, but clinical data are limited, concerns exist about the development of resistance with monotherapy, and no parenteral formulation is available in the United States. Although control data are lacking, combination therapy is being used in this setting with the goals of increasing efficacy and decreasing the emergence of resistance.

Resistance to fluoroquinolones usually is due to alterations of the target site (DNA gyrase and/or topoisomerase IV), with or without decreased permeability, active efflux, or protection of the target site. Resistance to this drug class 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 resistant to fluoroquinolones. At present, quinolones should be considered unreliable as empirical therapy for infections due to GNB in critically ill patients.

In this era of increasing antimicrobial resistance, it is critical to culture the local site of infection before the initiation of antimicrobial therapy and, for systemically ill patients, to obtain blood samples for culture. Antimicrobial resistance may not always be identified by in vitro testing; therefore, it is important to assess the clinical response to treatment. Moreover, as discussed above, resistance may emerge during therapy through the induction or stable derepression of AmpC β-lactamases. In addition, drainage of abscesses, resection of necrotic tissue, and removal of infected foreign bodies are often required for cure. GNB are commonly involved in polymicrobial infections, in which the role of each individual pathogen is uncertain (Chap. 201). Although some GNB are more pathogenic than others, it is usually prudent, if possible, to design an antimicrobial regimen active against all of the GNB identified, because each is capable of pathogenicity in its own right. Lastly, for patients treated initially with a broad-spectrum empirical regimen, the regimen should be de-escalated as expeditiously as possible once susceptibility results are known and the patient has responded to therapy.

PREVENTION

(See also Chap. 168) Avoidance of inappropriate antimicrobial use is a key measure in preventing infections due to antimicrobial-resistant strains and the further development of antimicrobial resistance. Antimicrobial stewardship programs should be adopted to facilitate achievement of this goal. Diligent adherence to hand-hygiene protocols by health care personnel, cleaning/disinfection of objects that come into contact with patients (e.g., stethoscopes and blood pressure cuffs), and contact precautions should be implemented for patients colonized or infected with carbapenem-resistant (and perhaps other XDR) GNB. Avoidance of the use of indwelling devices (e.g., urinary and intravascular catheters, endotracheal tubes) and, when such devices are necessary, placement according to an appropriate protocol decrease infection risk. Likewise, protocols for daily use evaluation and removal as soon as possible should be implemented. Patient positioning (e.g., head of bed at ≥30°) and good oral hygiene decrease the incidence of pneumonia among ventilated patients. Increasing data support the implementation of universal decolonization to prevent infection in ICU patients.

ESCHERICHIA COLI INFECTIONS

Strains of *E. coli* are united by a core genome of ~2000 genes. A strain's ability to cause infections and the nature of such infections are defined by ancillary genes that encode various virulence factors. This experiment of nature is fluid and ongoing, as demonstrated by the recent evolution of Shiga toxin–producing enteroaggregative *E. coli*.

COMMENSAL STRAINS

For the most part, commensal *E. coli* variants, which constitute the bulk of the normal facultative intestinal flora in most humans, confer benefits to the host (e.g., resistance to colonization with pathogenic organisms). These 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 presence of an aggravating factor, such as a foreign body (e.g., a urinary catheter), host compromise (e.g., local anatomic or functional abnormalities, such as urinary or biliary tract obstruction or systemic 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 community-acquired and health care–associated bacterial infections. The emerging propensity of these strains to acquire new antimicrobial resistance mechanisms (e.g., ESBL and carbapenemase production) has posed challenges in managing ExPEC infection. One clonal group—ST131, the members of which are usually resistant to fluoroquinolones and increasingly express an ESBL (CTX-M)—has undergone global dissemination.

Like commensal *E. coli* (but in contrast to intestinal pathogenic *E. coli*), ExPEC strains are often found in the intestinal flora of healthy individuals and 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 genes encoding diverse extraintestinal virulence factors that enable the bacteria to cause infections outside the gastrointestinal