More than 1000 β-lactamases (BL) exist in gram-negative bacteria (GNB). Many of the most clinically important and recently identified BLs include extended spectrum β-lactamases (ESBLs), AmpC β-lactamases (AmpC-BL), Klebsiella pneumoniae carbapenemases (KPC), and the metallo-β-lactamases (MBLs).1 Many multidrug-resistant bacteria produce multiple BLs, including combinations of ESBLs and carbapenemases, as well as nonenzyme resistance mechanisms (eg, porin loss, efflux pumps).1

Two classification schemes exist for BLs: Ambler classes A through D, based on amino acid sequence homology, and the Bush-Jacoby groups 1 through 4, based on molecular differences (Table 1).

**Carbapenemases**

Carbapenemases are enzymes that inactivate carbapenems and sometimes other classes of β-lactams. This subset of BLs belongs to Ambler classes A, B, and D. Each class has specific enzyme types based on molecular differences (Table 1). Carbapenemases are found in Enterobacteriaceae, Pseudomonas spp., and Acinetobacter spp. The majority of genes controlling carbapenemase production are transferable by plasmids. For the most part, BL-inhibitors, such as clavulanic acid, tazobactam, and sulbactam, are inactive against carbapenemases.

**Ambler Class A Carbapenemases**

Serine carbapenemase include many subtypes (Table 1). Gene(s) that control their production can be located on the bacterial chromosome or a plasmid. Serine carbapenemases can decrease bacterial susceptibility to all β-lactams. Imipenem and cefoxitin induce chromosomal-based serine carbapenemase production, but not plasmid-borne production. This induction confers resistance to carbapenems, penicillin, and aztreonam, but not to extended spectrum β-lactams.

Presently in the United States, about 4% of Escherichia coli and 10% of K. pneumoniae produce carbapenemases with the percentage varying by geographical area. KPC is the most common carbapenemase in the United States. Although first recognized in K. pneumoniae, KPCs are now distributed in other Enterobacteriaceae. KPC-producing isolates are generally resistant to quinolones and aminoglycosides but usually susceptible to colistin and tigecycline. Of 344 KPC isolates tested by the Center for Disease Control and Prevention between January 2007 and October 2009, 312 (91%) had colistin minimum inhibitory concentrations (MICs) <2 μg/mL and 304 (88%) had a tigecycline MIC of ≤2 μg/mL; 2/344 were resistant to colistin and tigecycline.2 Carbapenem and colistin heteroresistance is reported in carbapenem-producing K. pneumoniae.3,4

**Ambler Class B Carbapenemases**

Class B carbapenemases are referred to as MBLs because they require the presence of zinc to function. Due to this zinc dependency, chelators such as EDTA inhibit MBL activity. Until 2009, the MBL carbapenemase subtype Verona integron-borne metallo beta-lactamase was the most widely disseminated. In 2009, a novel MBL subtype was recognized in a K. pneumoniae isolate from a Swedish patient originally treated in New Delhi, India.5 The enzyme was named NDM-1 (New Delhi MBL-1). NDM-1 is now disseminated worldwide in Enterobacteriaceae and other GNB. The frequent association of this gene with a promiscuous plasmid enhances its spread. In June 2011, a Providencia stuartii isolate containing NDM-1, enzyme was reported in a US service person in Afghanistan.6 The term “superbug” is used to describe bacteria carrying the NDM-1 because these bacteria are resistant to most antibacterials with perhaps the exceptions of colistin, fosfomycin, and tigecycline. Although infections with bacteria possessing the NDM-1 enzyme can be fatal, NDM-1 bacterial colonization also occurs without disease. Between January 2009 and February 2011, the CDC has recognized 7 NDM-1-producing Enterobacteriaceae in the United States.

**Ambler Class D Carbapenemases**

This group of carbapenemases is of the oxacillinase (OXA) enzyme type. They have weak activity against carbapenems and are found primarily in Pseudomonas aeruginosa, Acinetobacter baumannii, and rarely in isolates of Enterobacteriaceae from the United States. OXA CPM genes can be located on bacterial chromosomes or plasmids. Activity of OXA carbapenemases can be increased by upstream elements that control gene expression. The major concern with OXA carbapenemases is their ability to rapidly mutate and expand their spectrum of activity. In the United States, >50% of A. baumannii are resistant to carbapenems due to production of OXA class carbapenemases.

**AmpC β-lactamase**

AmpC BLs belong to Ambler Class C. Genes for the production of AmpC-BL can exist on bacterial chromosomes or plasmids in P. aeruginosa and many Enterobacteriaceae. AmpC genes on the bacterial chromosome produce low levels of BLs (“repressed”) but can become “de-repressed” by induction by antibacterials such as cefoxitin.7 When “de-repressed,” the BL is hyperproduced. AmpC genes located on plasmids constitutively produce the BL. AmpC-BL has minimal activity against carbapenems and monobactam (eg, aztreonam). However, when AmpC-BL is combined with decreased susceptibility due to porin and efflux mechanisms, clinically significant levels of resistance are achieved.

**Laboratory Detection of Carbapenemases and AmpC β-lactamases**

Most clinical laboratories remain dependent on phenotypic methods to detect bacteria capable of producing carbapenemase and AmpC-BL. Techniques that rely
Upon synergistic activity between a key substrate and a selective inhibitor in broth dilution, disk diffusion, or commercial systems are used. The most definitive system to detect ability to produce carbapenemase and AmpC BL is gene amplification by polymerase chain reaction (PCR). Multiplex PCR can be used to detect a number of genes at one time. Matrix-associated laser desorption/ionization time of flight mass spectrometry, which detects BL-degraded fragments of antibiotics, is a new method that shows promise. At this time neither PCR nor matrix-associated laser desorption/ionization time of flight are methods available to most microbiology laboratories.

The modified Hodge test is often used to detect carbapenem resistance in Enterobacteriaceae. Its major disadvantage is that results are not timely enough to assist with choosing antimicrobial therapy in early stages of care. This test only detects resistance due to carbapenemases and is only validated for Enterobacteriaceae.

To address this time frame issue, lowering the Enterobacteriaceae susceptibility breakpoints for the carbapenems has been proposed. This is similar to the approach taken for ESBL-producing Enterobacteriaceae. This works because most bacteria capable of producing carbapenemases and ESBLs have higher MICs than those that do not.

**Treatment**

The number of antimicrobial agents reliably effective against these often multi-drug-resistant organisms is very limited. Carbapenems can be used to treat infections due to AmpC-BL-producing organisms. Cefepime is a poor inducer of AmpC-BL and may have a role in treating such infections, but this is not always clear.

**REFERENCES**