tivity, especially against gram-negative organisms such as *Pseudomonas* and *Proteus* species and *E. coli*. For pseudomonal infections, one of these drugs is usually given concomitantly with an aminoglycoside or a fluoroquinolone (see Chap. 35). Carbenicillin is available as an oral formulation for UTI or prostatitis caused by susceptible pathogens. The other drugs are usually given by intermittent IV infusion, although most can be given IM.

Penicillin/Beta-Lactamase Inhibitor Combinations

Beta-lactamase inhibitors are drugs with a beta-lactam structure but little antibacterial activity. They bind and inactivate the beta-lactamase enzymes produced by many bacteria (eg, *E. coli*, *Klebsiella*, *Enterobacter*, and *Bacteroides* species, and *S. aureus*). When combined with a penicillin, the beta-lactamase inhibitor protects the penicillin from destruction by the enzymes and extends the penicillin's spectrum of antimicrobial activity. Thus, the combination drug may be effective in infections caused by bacteria that are resistant to a beta-lactam antibiotic alone. Clavulanate, sulbactam, and tazobactam are the beta-lactamase inhibitors available in combinations with penicillins.

Unasyn is a combination of ampicillin and sulbactam available in vials with 1 g of ampicillin and 0.5 g of sulbactam or 2 g of ampicillin and 1 g of sulbactam. **Augmentin** contains amoxicillin and clavulanate. It is available in 250-, 500-, and 875-mg tablets, each of which contains 125 mg of clavulanate. Thus, two 250-mg tablets are not equivalent to one 500-mg tablet. **Timentin** is a combination of ticarcillin and clavulanate in an IV formulation containing 3 g ticarcillin and 100 mg clavulanate. **Zosyn** is a combination of piperacillin and tazobactam in an IV formulation. Three dosage strengths are available, with 2 g piperacillin and 0.25 g tazobactam, 3 g piperacillin and 0.375 g tazobactam, or 4 g piperacillin and 0.5 g tazobactam.

CEPHALOSPORINS

Cephalosporins are a widely used group of drugs that are derived from a fungus. Although technically cefoxitin and cefotetan (cephamycins derived from a different fungus) and loracarbef (a carbacephem) are not cephalosporins, they are categorized with the cephalosporins because of their similarities to the group. Cephalosporins are broad-spectrum agents with activity against both gram-positive and gram-negative bacteria. Compared with penicillins, they are in general less active against gram-positive organisms but more active against gram-negative ones.

Once absorbed, cephalosporins are widely distributed into most body fluids and tissues, with maximum concentrations in the liver and kidneys. Many cephalosporins do not reach therapeutic levels in CSF; exceptions are cefuroxime, a second-generation drug, and the third-generation agents. These drugs reach therapeutic levels when meninges are inflamed. Most cephalosporins are excreted through the kidneys. Exceptions include cefoperazone, which is excreted in bile, and ceftriaxone, which undergoes dual elimination via the biliary tract and kidneys. Cefotaxime is primarily metabolized in the liver to an active metabolite, desacetylcefotaxime, which is eliminated by the kidneys.

First-Generation Cephalosporins

The first cephalosporin, cephalothin, is no longer available for clinical use. However, it is used for determining susceptibility to first-generation cephalosporins, which have essentially the same spectrum of antimicrobial activity. These drugs are effective against streptococci, staphylococci (except methicillin-resistant *S. aureus*), *Neisseria*, *Salmonella*, *Shigella*, *Escherichia*, *Klebsiella*, and *Bacillus* species, *Corynebacterium diphtheriae*, *Proteus mirabilis*, and *Bacteroides* species (except *Bacteroides fragilis*). They are not effective against *Enterobacter*, *Pseudomonas*, and *Serratia* species.

Second-Generation Cephalosporins

Second-generation cephalosporins are more active against some gram-negative organisms than the first-generation drugs. Thus, they may be effective in infections resistant to other antibiotics, including infections caused by *Hemophilus influenzae*, and *Klebsiella* species, *E. coli*, and some strains of *Proteus*. Because each of these drugs has a different antimicrobial spectrum, susceptibility tests must be performed for each drug rather than for the entire group, as may be done with first-generation drugs. Cefoxitin (Mefoxin), for example, is active against *B. fragilis*, an anaerobic organism resistant to most drugs.

Third-Generation Cephalosporins

Third-generation cephalosporins further extend the spectrum of activity against gram-negative organisms. In addition to activity against the usual enteric pathogens (eg, *E. coli*, *Proteus* and *Klebsiella* species), they are also active against several strains resistant to other antibiotics and to first- and second-generation cephalosporins. Thus, they may be useful in infections caused by unusual strains of enteric organisms such as *Citrobacter*, *Serratia*, and *Providencia*. Another difference is that third-generation cephalosporins penetrate inflamed meninges to reach therapeutic concentrations in CSF. Thus, they may be useful in meningeal infections caused by common pathogens, including *H. influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Although some of the drugs are active against *Pseudomonas* organisms, drug-resistant strains may emerge when a cephalosporin is used alone for treatment of pseudomonal infection.

Overall, cephalosporins gain gram-negative activity and lose gram-positive activity as they move from the first to