CHAPTER **30**

ANTIBIOTIC UPDATE

Crista Gredlein, D.P.M.
Stephen V. Corey, D.P.M.

Since the advent of antimicrobial therapy, new agents continue to be synthesized and used clinically. The emergence of bacterial resistance increases the necessity for new antibiotic development or improvement of the activity of agents presently available. In the last few years, there have been several new antimicrobial agents approved and released for clinical use in the United States. All are related to the already existing classes of antibiotics, but most have an extended spectrum of activity compared to others of the same class. Several of these newer agents are merely duplicates of the older related compounds, but many prove to have additional advantages in antimicrobial chemotherapy.

This article reviews the new antimicrobial agents that are presently in use in the United States. Agents belonging to the cephalosporin, penicillin, carbapenem, quinolone, and macrolide classes have recently been approved and released for clinical use.

CEPHALOSPORINS

All cephalosporins have the same basic chemical structures, and modification of this beta-lactam ring enables newly-developed agents to possess slightly different characteristics. Cephalosporins are classified into groups or generations based primarily on their antimicrobial activity. In general, it can be stated that the first generation agents possess the greatest gram-positive coverage, second generation drugs have activity against *Haemophilus influenza,* third generation agents have less gram-positive, but greater gram-negative activity, and the new fourth generation cephalosporin has added activity verses *Pseudomonas aeruginosa*. Although this classification is merely a generalization, it may be used as the framework by which antimicrobial therapy is initiated.

Cefepime (Maxipime®), the first fourth generation cephalosporin, was recently FDA approved and released for use. Its spectrum of activity includes those gram-negative and gram-positive organisms that are susceptible to the third generation cephalosporins. In addition, it has been classified as a fourth generation agent because of its extended coverage against gram-negative bacilli, which includes *Pseudomonas aeruginosa* and certain Enterobacteriaceae. Cefepime has been shown to be comparable to cefotaxime in its activity against staphylococci and nonenterococcal streptococci, and comparable to ceftaxidime against *Pseudomonas aeruginosa.* As with the third generation cephalosporins, this fourth generation agent is ineffective in the treatment of enterococci and methicillin-resistant *Staphylococcus aureus/ epidermidis*. The recommended dosing of cefepime in adults is 0.5 grams to 2.0 grams administered intravenously every twelve hours. Side effects, although rare, have been skin rash, diarrhea and local reactions related to the intravenous catheter site.

Ceftibuten (Cedax®) is a new extended spectrum cephalosporin released for oral use. Its activity has been extended to include *Haemophilus influenza* and some other gram-negative bacilli. However, it is not active against *Pseudomonas aeruginosa* and is of little use in the treatment of infections caused by *Staphylococcus aureus.* Ceftibuten has been approved for the treatment of chronic bronchitis, acute otitis media and acute pharyngitis/tonsillitis. Because of its relative inactivity against staphylococci and pseudomonas in addition to its indicated uses, ceftibuten therapy is very limited in the treatment of lower extremity infections.

PENICILLINS

Pipercillin/tazobactam (Zosyn®) combines the effect of a penicillin and a beta-lactam inhibitor. This combination antibiotic is active against gram-positive aerobes including methicillin sensitive *Staphylococcus aureus* and streptococci, gram-negative aerobes including *Escherichia coli* and

Haemophilus influenza and many anaerobes including *Bacteroides fragilis*. In addition, piperacillin alone is the most active of all penicillins against *Pseudomonas aeruginosa*. The ratio of piperacillin to tazobactam is 8:1 and is administered intravenously at a dosage of 3.375 grams every six hours. It is approved for the treatment of community-acquired pneumonia, intra-abdominal, pelvic, skin, and soft tissue infections. Diarrhea is the most common adverse reaction and an excess sodium load may result from high doses. Zosyn® is useful as empiric therapy for severe diabetic foot infections because its spectrum of activity is adequate for the polymicrobial nature of these infections.

Amoxicillin/clavulanic acid (Augmentin®), is not a new antimicrobial agent, however a new dosing regimen has recently been introduced by the manufacturer. It was actually the first oral combination of a penicillin and a beta-lactamase inhibitor. It is indicated for the treatment of lower respiratory, skin and soft tissue infections including the treatment of animal or human bite wounds, and diabetic foot ulcerations. Amoxicillin alone is active against many gram-negative and gram-positive organisms, and clavulanic acid confers additional activity verses *Staphylococcus aureus* (not MRSA) and many anaerobes. The new recommended dose is 875 mg taken orally twice a day, although the older preparations of 250 and 500 mg are still available.

CARBAPENEMS

Meropenem is a new agent belonging to the carbapenem class that is similar to imipenem in most aspects. It is a very broad spectrum agent that covers most gram-positive cocci, gram-negative bacilli and many anaerobes. It has activity against methicillin-sensitive *Staphylococcus aureus, Bacteroides fragilis* and *Pseudomonas aeruginosa*. Unlike imipenem, this agent does not require the addition of a renal dehydropeptidase inhibitor. Meropenem is indicated for the treatment of intra-abdominal and gynecologic infections, pleuro-pulmonary infections and moderate to severe polymicrobial soft tissue infections. The dosage is 500 mg. to 1 gram given intravenously every eight hours. Side effects include gastrointestinal upset, nausea, and occasional elevation of liver function tests, but unlike imipenem, seizures rarely occur as a result of meropenem therapy.

QUINOLONES

The fluoroquinolones are a relatively new class of antibiotics, of which two new additions, levofloxacin (Levoquin®) and sparofloxacin (Zagam®), recently received FDA approval for clinical use in the United States. Like the older quinolones, levofloxacin and sparfloxacin are active against many gram-negative bacilli including *Pseudomonas aeruginosa*. But in addition, these newer compounds are more active against gram-positive bacteria, including enterococci, pneumococci and staphylococci (not MRSA). Sparfloxacin is more potent against anaerobes than other quinolones, although it is not indicated for that use. Both agents have been shown to be effective in the treatment of urinary tract infections, sexually transmitted diseases, osteomyelitis, septic arthritis, skin and soft tissue infections, sinusitis and chronic bronchitis. The dosage of sparofloxacin is an initial dose of 200 mg. followed by 100 mg. daily, taken orally. The dosage of levofloxacin is 500 mg. daily, administered either orally or intravenously.

Adverse effects are rare, but when they do occur the most common are gastrointestinal upset, headache, and skin or allergic reactions. In addition, quinolones as a class have been shown to have a detrimental effect on developing cartilage, therefore are contraindicated for use in children and pregnant women. Sparofloxacin has been associated with photosensitivity, so patients should be warned against sun exposure while taking this drug, and for the five days following cessation of therapy. Both of these newer agents provide a useful spectrum of activity, and are a good adjunct for the conversion from intravenous to oral antimicrobial therapy.

MACROLIDS

The new macrolid antibiotics now available are clarithromycin (Biaxin®), azithromycin (Zithromax®) and dirithromycin (Dynabac®). All of these agents are chemically related to erythromycin, but possess slight alterations in the spectrum of activity. Clarithromycin has better gram-positive coverage, and azithromycin has greater activity against gram-negative bacteria including *Escherichia coli, Haemophilis influenza* and Klebsiella. Dirithromycin is essentially the same in its antimicrobial activity as erythromycin, with the added benefit of a once daily dosing regimen.

These agents are indicated for the treatment of lower respiratory infections, many sexually-transmitted diseases, streptococcal pharyngitis, and for skin and soft tissue infections, especially when the causative organism is *Staphylococcus aureus.* Each of these new macrolid antibiotics are available in oral preparations only. Azithromycin is dosed 500 mg. initially, followed by 250 mg. daily for the next four days. The dosage of clarithromycin is 250 to 500 mg. twice a day for one week. As mentioned previously, dirithromycin has the advantageous dosing schedule of 500 mg. taken once per day for one week. These newer agents have the same side effects as erythromycin, which include reversible hearing disturbances, gastrointestinal upset, diarrhea, nausea and vomiting, but with each occurring to a much lesser degree.

TEICOPLANIN

Although not currently available in the United States, teicoplanin, a glycopeptide agent similar to vancomycin, has widespread use throughout Europe. Its spectrum of activity is limited to gram-positive aerobic and anaerobic bacteria including methicillin sensitive *Staphylococcus aureus* and methicillin resistant *Staphylococcus aureus.* Teicoplanin is more active than vancomycin verses all streptococci, including enterococci. For minor infections (i.e. skin and soft tissue) a 400 mg. intravenous loading dose is given, followed by 200 to 400 mg. daily for maintenance levels. Major infections (i.e. septic arthritis and osteomyelitis) require two loading doses of 400 to 800 mg. every twelve hours, followed by a maintenance dose of 400 to 800 mg. daily. Unlike vancomycin, teicoplanin may be administered as an intravenous bolus over a five minute period because the occurrence of red man syndrome or anaphylactoid reactions are extremely rare. The most common adverse effects of teicoplanin therapy are injection site intolerance, skin rash and rarely transient abnormalities in liver function tests.

BIBLIOGRAPHY

Ambrose PG, Owens RC, Quintiliani R, Nightingale CH: New generations of quinolones: with particular attention to levofloxacin. *Conn Med* 61(5):269-272,1997.

Burke AC, Klein NC: Cefepime *Med Clin North Am* 79(4): 721-731,1995.

Ceftibuten. A new oral cephalosporin. *Med Lett Drugs Ther* 38:23-24,1996.

Choi C: Antibiotics: What s New? *Comp Ther* 23(6):378-383, 1997.

Dirithromycin. *Med Lett Drugs Ther* 37(962):109-110,1995.

Fish DN, Singletary TJ: Meropenem, a new carbapenem antibiotic. *Pharmacotherapy* 17(4):644-669,1997.

Goldstein EJC: Possible role for the new fluoroquinolones (levofloxacin, grepafloxacin, trovafloxacin, clinofloxacin, sparfloxacin, and DU-6859a) in the treatment of anaerobic infections: Review of current information on efficacy and safety. *Clin Infect Dis* 23(Suppl 1):25-30,1996.

Klein NC, Burke CA: Third generation cephalosporins. *Med Clin North Am* 79(4):705-719, 1995.

Norrby SR: Carbapenems. *Med Clin North Am* 79(4):745-759,1995.

Sanders WE, Sanders CC: Pipercillin/Tazobactam: A critical review of the evolving clinical literature. *Clin Infect Dis* 22:107-123,1996.

Schlossberg D: Azithromycin and Clarithromycin. *Med Clin North Am* 79(4):803-815,1995.

Schmidt J, Pollack CV: Antibiotic use in the emergency department. 111. The quinolones, new beta-lactams, betalactam combination agents, and miscellaneous antibiotics. *J Emer Med* 14(4):483-496,1996.

Shea KW, Cunha BA: Teicoplanin. *Med Clin North Am* 79(4):833-843,1995.

Sparfloxacin and Levofloxacin. *Med Lett Drugs Ther* 39(999):41-43,1997.

Stein GE, Havlichek DH: Sparfloxacin: Potential clinical and economic impact in the treatment of respiratory infections. *Pharmacotherapy* 17(6):1139-1147,1997.

Tan JS, Wishnow RM, Talan DA, Duncanson FP, Norden CW: Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multi-center study of piperacillin-tazobactam versus ticarcillin-clavulanic acid. *Antimicrob Agents Chemother* 3:1580-1586,1993.