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Antimicrobial Chemotherapy in the Intensive Care Unit

Louis D. Saravolatz, MD*

Antimicrobial chemotherapy represents a major tool for the intensivist in rescuing the critically ill patient. Because nosocomial infection is a frequent medical complication, afflicting 12.4% to 50% of patients, it behooves the intensive care specialist to utilize antimicrobial agents judiciously and effectively (1, 2). Nowhere in the hospital is the clinician’s knowledge of drug therapy more challenged than in the intensive care unit. Patients present alterations in pharmacokinetics due to changes in drug absorption, distribution, metabolism, and excretion. Further confounding the treatment of intensive care unit infectious diseases is the occurrence of both unusual and resistant organisms requiring the determination of whether to use newer agents or older agents which may be effective for a new indication. Still another clinical dilemma is recognizing adverse effects attributable to antimicrobial chemotherapy in a patient receiving multiple classes of drugs and who has multiple pathophysiologic processes that have signs and symptoms similar to drug side effects. This article reviews antimicrobial agents utilized in the intensive care unit in relation to their mechanism of action, in vitro activity, efficacy, pharmacokinetics, and adverse effects.

Aminoglycosides

Aminoglycosides have been available since the isolation of streptomycin in 1944 (3). Although still used in the treatment of mycobacteria, plague, brucellosis, and tularemia and as part of the combination therapy in streptococcal endocarditis, streptomycin is rarely used in the intensive care setting. The major aminoglycosides utilized include gentamicin, tobramycin, and amikacin. These drugs are presently needed to treat the most serious intensive care unit gram-negative infections, except meningitis and urinary tract infection. In addition, aminoglycosides have some role in combination therapy of gram-positive infections.

Mechanism of action

The aminoglycosides are bactericidal agents that interfere with protein synthesis. These agents bind to the 30S subunit of bacterial ribosomes. The consequence of this binding is the misreading of the genetic code of DNA onto the messenger RNA (transcription); thus, the wrong amino acids are incorporated into the growing peptide chains and faulty bacterial proteins are produced.

Spectrum of in vitro activity

Aminoglycosides are active primarily against aerobic gram-negative bacilli, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Of note is the absence of activity of aminoglycosides against bacteria in anaerobic conditions. Thus, aminoglycosides are inactive against anaerobes or conditions in which bacteria have a low electrical potential, such as in abscesses (4). Additionally, *Listeria monocytogenes* and streptococci, including *Streptococcus pneumoniae*, are generally resistant to clinically achievable serum concentrations of aminoglycosides.

Table 1 provides the activity of gentamicin, tobramycin, and amikacin against a large number of gram-negative bacilli. The activity of gentamicin parallels that of tobramycin, except in *Pseudomonas aeruginosa* where tobramycin demonstrates greater activity than gentamicin, and in *Serratia marcescens* where gentamicin is more active than tobramycin. These results are similar to those of most surveys done throughout the United States. However, a difference noted in some areas, including our institution, has been the enhanced susceptibility of *Acinetobacter calcoaceticus var. anitratus*, where tobramycin usually has greater activity than gentamicin (5). Also, amikacin possesses as much or more activity against all strains of bacteria tested.

Pharmacokinetics

Aminoglycosides are not absorbed when given orally and thus are used as bowel preparations to suppress bacterial flora of the gastrointestinal tract prior to surgery or in cancer patients who are placed in controlled environments such as laminar flow units. The drug may be given via intramuscular or intravenous routes. The latter is preferred in order to achieve higher peak serum concentrations. Peak serum concentrations are usually...
achieved 1 hour after an intramuscular dose and 30 minutes after an intravenous infusion. Desired peak concentrations are generally 4 to 10 μg/mL for gentamicin and tobramycin and 25 to 35 μg/mL for amikacin. A predose (trough) concentration for aminoglycosides should be < 2 μg/mL for gentamicin and tobramycin and < 8 μg/mL for amikacin. The peak concentration has been suggested as a predictor of clinical outcome, and the trough levels correlate best with toxicity. In the healthy adult with normal renal function, the half-life is 1.5 to 3.5 hours. The most frequent conditions requiring alterations of aminoglycoside dosages include the extremes of age as well as kidney disease; however, other conditions such as obesity, protein-calorie malnutrition, fever, and severe burns may significantly alter aminoglycoside levels and warrant careful monitoring of serum concentrations. In patients with normal renal function, a loading dose of 1.5 to 2 mg/kg for gentamicin or tobramycin and 7.5 to 8 mg/kg for amikacin will give the desired peak levels. The loading dose should be the same regardless of the degree of renal dysfunction. After the loading dose, the maintenance dose in patients with normal renal function is usually 1.5 to 2 mg/kg every 8 hours for gentamicin and tobramycin and 7.5 mg/kg every 12 hours for amikacin. In the case of renal dysfunction, the daily dosage may be reduced by multiplying it by the ratio of the patient’s creatinine clearance to the normal creatinine clearance. For example, using the equation of Cockcroft and Gault (6),

\[
C_\text{cr} (\text{mL/min}) = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Cr}} \times 72
\]

for a 40-year-old man with a weight of 70 kg and a serum creatinine of 5 mg/dL, the \(C_\text{cr}\) would be 20 mL/min and the normal \(C_\text{cr}\) should be 100 mL/min. Thus, the daily maintenance dose would be 20 mL/min divided by 100 mL/min \(\times 4.5\) to 6 mg/kg/day = 0.9 to 1.2 mg/kg/day. This dose could then be given in one of two ways: reduce the dose and maintain the same interval or give the dose at less frequent intervals. There is no evidence to support better efficacy with either approach; however, dose intervals should be reasonably convenient for nursing administration. Despite extensive experience and even modifications of nomograms, discrepancies may arise between desired and actual serum levels. Thus, frequent, carefully timed determinations are needed to assure adequate aminoglycoside levels in the critically ill patient with gram-negative sepsis.

Aminoglycosides do not penetrate all body sites equally. They do not achieve sufficient cerebrospinal fluid penetration in adults to cure patients even with inflamed meninges. Thus, these drugs have been replaced in the treatment of gram-negative meningitis by the third-generation cephalosporins.

Bronchial secretions are another important body site for penetration in the critically ill patient. Although studies have yielded variable results, concentrations in bronchial secretions are approximately 20% of mean plasma levels (7). Furthermore, the low pH of bronchial secretions may render aminoglycosides less active. Thus, when an aminoglycoside is used in gram-negative pneumonia, a second drug is essential to achieve sufficient bactericidal activity. Aminoglycosides are eliminated unchanged by the kidneys; therefore, hepatic insufficiency does not necessitate alteration in aminoglycoside dosing unless concomitant renal dysfunction is present.

### Efficacy in the intensive care unit

Despite the proliferation of newer and more active antimicrobial agents including the new beta-lactams, aminoglycosides are still considered the mainstay of therapy in gram-negative sepsis. These agents are almost always combined with beta-lactam antibiotics because of the additive or synergistic effect. In a study of over 400 episodes of bacteremia due to gram-negative bacilli, Anderson et al (8) showed that synergistic combinations of antibiotics had significantly higher response rates in seriously ill patients with rapidly or ultimately fatal disease, shock, or neutropenia compared to patients who received two nonsynergistic drugs. Aminoglycosides are considered interchangeable in terms of efficacy; however, in infection caused by *Pseudomonas aeruginosa*, tobramycin is preferred over gentamicin because of greater inhibitory activity. This may be significant in the intensive care unit, where *Pseudomonas aeruginosa* is the leading cause of hospital-acquired pneumonia (9). As resistance rates to

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Strains</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acinetobacter calcoaceticus</em></td>
<td>320</td>
<td>43</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>156</td>
<td>81</td>
<td>79</td>
<td>100</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>6,083</td>
<td>98</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td>203</td>
<td>95</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>483</td>
<td>88</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1,122</td>
<td>93</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1,837</td>
<td>71</td>
<td>84</td>
<td>94</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>195</td>
<td>90</td>
<td>65</td>
<td>97</td>
</tr>
</tbody>
</table>

*Data collected in 1990 in collaboration with E. Mezger, MD, Director, Microbiology Laboratory, Henry Ford Hospital.*
gentamicin and tobramycin increase, amikacin may be used to treat specific infections. However, with increased usage, amikacin resistance will also occur. In an effort to preserve the effectiveness of amikacin, many infectious disease specialists recommend restricting use of this agent.

**Adverse effects**

Otoxicity has been reported with comparable frequency for all three aminoglycosides. Vestibular damage is more often associated with gentamicin and tobramycin, and cochlear damage with amikacin. Otoxicity may be increased by preexisting renal impairment, prior therapy with ototoxic drugs, therapy for more than 10 days, high serum aminoglycoside levels, and concomitant administration of ethacrynic acid, furosemide, mannitol, and possibly other diuretics. If patients will receive aminoglycoside therapy for longer than three weeks, as in the case of endocarditis or osteomyelitis, consideration should be given to monitoring otoxicity with vestibular or audiometric testing. However, the ambience of the intensive care unit is not conducive to the performance of either of these tests.

Nephrotoxicity is the major toxicity of aminoglycosides, occurring in 2% to 10% of patients (10,11). Nephrotoxicity occurs in the kind of patient frequently hospitalized in intensive care units, specifically those who are debilitated, elderly, have contracted intravascular volumes, or have previous renal dysfunction. The studies published to date suggest that tobramycin is less nephrotoxic than gentamicin. Since aminoglycoside nephrotoxicity is at least partially reversible, studies have concluded that the lower nephrotoxic potential must be weighed against the significant cost differential of these compounds. Thus, in patients with preexisting renal impairment, it may be prudent to use tobramycin. In monitoring nephrotoxicity, the serum creatinine is an insensitive parameter. Therefore, monitoring urinary cast excretion, which will increase before the serum creatinine, is a much more sensitive predictor of aminoglycoside-induced nephrotoxicity.

Neuromuscular blockade is of concern in the critical care setting. The result of this may be flaccid paralysis, respiratory depression, and dilated pupils. Aminoglycosides may act at two different sites in causing this blockade (12). Though neuromuscular blockade is considered a rare event, it may be enhanced by conditions that are sometimes not uncommon to the intensive care unit, such as severe hypocalcemia, neuromuscular disease, magnesium administration, botulism, ether anesthesia, d-tubocurarine, succinylcholine, and gallamine triethiodide (13,14).

The neuromuscular blockade has been associated with most routes of administration and is related to the presence of high concentrations of the drug at the neuromuscular junctions. Thus, rapid bolus intravenous infusion or instillation of highly concentrated solutions into the pleural or peritoneal space will enhance the likelihood of achieving such high concentrations. Treatment of the neuromuscular blockade should include avoidance of clinical situations that lead to high aminoglycoside concentrations, administration of 0.25 mg neostigmine intravenously every 30 minutes until respiratory paralysis is reversed, or the intravenous administration of 5.0 g of calcium gluconate (15,16). Although both calcium gluconate and neostigmine have been found to be effective in reversing aminoglycoside-induced apnea, calcium gluconate is preferred since the benefit of neostigmine has been variable. Also, repeated doses of calcium and continued ventilatory support may be necessary in reversing the neuromuscular blockade.

Other reactions that have been reported include eosinophilia, rash, fever, leukopenia, and transient elevation of liver enzymes (17). These reactions are rare and seldom serious.

**Cephalosporins**

The cephalosporin family of drugs represents the group of antimicrobial agents with the largest number of new additions. These drugs are compounds that are widely prescribed throughout the hospital, including the intensive care units. The number of available agents has increased because they are safe and effective.

**Mechanism of action**

Cephalosporins are bactericidal drugs that act by binding to penicillin-binding proteins (PBPs) that are associated with the cell membrane of bacterial cells (18). The PBPs are enzymes, endopeptidases, transglycosylases, transpeptidases, and carboxypeptidases that are necessary for the biosynthesis of peptidoglycan, which is the backbone of bacterial cell walls. When binding with the PBPs occurs, autolysins may be released resulting in cell death. If a bacterium is deficient in the autolysins, then the growth may only be inhibited and the organism is referred to as tolerant to the antibiotic. Since at least seven different PBPs exist, there may be some rationale in combining beta-lactam drugs that act on different PBPs in order to achieve a synergistic effect. On the other hand, some beta-lactam agents may be antagonistic when combined and thus synergy studies need to be performed in order to identify appropriate combination therapy (19).

**Spectrum of in vitro activity**

Cephalosporins have been classified in terms of "generations" which are based on in vitro activity. Table 2 lists the available agents in each of the generations. The first-generation agents have good activity against gram-positive cocci, except Enterococcus faecalis, methicillin-resistant Staphylococcus aureus, and Staphylococcus epidermidis. All generations of cephalosporins have good activity against Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis. The second-generation agents show only slightly greater activity against gram-negative organisms susceptible to first-generation cephalosporins. However, a word of caution is needed about the greater gram-negative activity of cefamandole. Some organisms, especially Enterobacter species, emerge resistant to cefamandole after being susceptible initially (20). This phenomenon is due to the repression of chromosomally-mediated beta-lactamase. For this reason, cefamandole should never be used as the sole agent in the therapy of serious Enterobacter infections.

Due to the in vitro activity of the second-generation cephalosporins, these agents have two major advantages. First, all second-generation cephalosporins have a minimal inhibitory con-
centrations of 90% of isolates (MIC90) of ≤ 6.0 μg/mL for Haemophilus influenzae while first-generation cephalosporins have a MIC90 of 10 μg/mL. Additionally, second-generation cephalosporins appear to be resistant to the β-lactamase that some strains of Haemophilus influenzae produce. Another advantage of the second-generation cephalosporins is considerably less than either first- or second-generation cephalosporins against the enterobacteriaceae and is more active than cefuroxime (Rocephin) and cefmenoxime (Cefmax). Cefoxitin, one of the second-generation cephalosporins, has excellent in vitro activity against Bacteroides fragilis. In general, cephalosporins are usually active against peptococcus, peptostreptococcus, fusobacterium, and clostridium (excluding Clostridium difficile). Most cephalosporins have poor activity against Bacteroides fragilis and variable activity against other Bacteroides species. The cephalosporins with the greatest activity against all anaerobes include cefoxitin, cefotetan, and cefizoxime.

**Pharmacokinetics**

Cephalosporins may be given via oral, intramuscular, or intravenous routes. Table 2 gives the usual dose and half-life of each agent. With doses listed in Table 2 for parenteral agents, serum concentrations may range from 60 to 270 μg/mL. These drugs are excreted primarily by renal mechanisms, either glomerular filtration and/or tubular secretion. Serum concentrations of agents that are not excreted by tubular secretion are not influenced by agents that block secretion, such as probenecid.

The cephalosporins generally have a significant prolonged half-life in the face of renal failure. The two exceptions are cefoperazone and ceftriaxone, which are the only cephalosporins whose half-life shows less than a twofold increase when the creatinine clearance is less than 10 mL/min. These drugs have a

---

**Table 2**  
Cephalosporins for Serious Infections

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Adult Dose</th>
<th>Half-life (M)</th>
<th>Second Generation</th>
<th>Adult Dose</th>
<th>Half-life (M)</th>
<th>Third Generation</th>
<th>Adult Dose</th>
<th>Half-life (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin (Ancef, Kefzol)</td>
<td>1 g/8 hr</td>
<td>1.5</td>
<td>Cefamandole (Mandol)</td>
<td>2 g/6 hr</td>
<td>0.8</td>
<td>Cefitazime (Claforan)</td>
<td>2 g/8 hr</td>
<td>1.7</td>
</tr>
<tr>
<td>Cephapirin (Cefadyl)</td>
<td>2 g/4 hr</td>
<td>0.6</td>
<td>Cefonicid (Monisid)</td>
<td>2 g/24 hr</td>
<td>4.4</td>
<td>Cefotaxime (Ceftizox)</td>
<td>2 g/6 hr</td>
<td>1.1</td>
</tr>
<tr>
<td>Cephalothin (Keflin)</td>
<td>2 g/4 hr</td>
<td>0.6</td>
<td>Ceforanide (Preceft)</td>
<td>1 g/12 hr</td>
<td>3.0</td>
<td>Ceftriaxone (Rocephin)</td>
<td>2 g/24 hr</td>
<td>8.0</td>
</tr>
<tr>
<td>Cephradine (Velesof, Anspor)</td>
<td>2 g/4 hr</td>
<td>1.3</td>
<td>Cefoxitin (Mefoxin)</td>
<td>2 g/6 hr</td>
<td>0.8</td>
<td>Cefmenoxime (Cefmax)</td>
<td>2 g/6 hr</td>
<td>1.0</td>
</tr>
<tr>
<td>Cefadroxil (Duricef, Ultracef)</td>
<td>1 g/12 hr</td>
<td>1.5</td>
<td>Cefuroxime (Zinacef)</td>
<td>1.5 g/8 hr</td>
<td>1.5</td>
<td>Cefotetan (Cefotan)</td>
<td>2 g/12 hr</td>
<td>4.0</td>
</tr>
<tr>
<td>Cephalexin (Keflex)</td>
<td>1 g/6 hr</td>
<td>1.3</td>
<td>Cefaclor (Ceclor)</td>
<td>1 g/8 hr</td>
<td>0.8</td>
<td>Moxalactam (Moxam)</td>
<td>2 g/8 hr</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(orally)</td>
<td></td>
<td></td>
<td>(orally)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cefmetazole (Elazone)</td>
<td>2 g/8 hr</td>
<td>1.3</td>
<td>Cefoperazone (Cefobid)</td>
<td>2 g/8 hr</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cefsurolid (Cefomonil)</td>
<td>2 g/8 hr</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cefazidime (Fortaz, Tazideme, Taricet)</td>
<td>2 g/8 hr</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Note: Cephalosporins are listed by generic names with proprietary names in parentheses.
dual route of excretion including an important hepatobiliary route. In general, dose adjustments for cephalosporins are needed in moderate to severe renal failure. The interval is prolonged to 1.5 to 2 times in moderate renal failure (creatinine clearance = 10 to 15 mL/min) and 3 to 4 times in severe renal failure (creatinine clearance < 10 mL/min). In the case of cefoperazone and ceftriaxone, no dose adjustment is needed for renal failure.

Cephalosporins tend to penetrate most body sites well, including bone, biliary tree, and the respiratory tree. However, cerebrospinal fluid activity varies with the intrinsic in vitro activity of each agent against the pathogens that cause meningitis. Approximately 5% to 20% of the serum level can be achieved in the cerebrospinal fluid when giving cefotizoxime, cefotaxime, ceftriaxone, ceftazidime, cefusulodin, or moxalactam to patients with inflamed meninges. These agents tend to be active against the organisms that cause gram-negative bacillary (including Haemophilus influenzae) meningitis. However, these agents are not appropriate for Listeria monocytogenes or group B streptococcal meningitis. Also, penicillin remains the treatment of choice for pneumococcal meningitis since failure has been observed with agents such as cefotaxime and moxalactam due to the inability to achieve cerebrospinal fluid concentrations in excess of the MIC for some strains of Streptococcus pneumoniae.

Efficacy in the intensive care unit
Cephalosporins are an extremely popular group of antimicrobial agents in the intensive care unit as well as in the rest of the hospital. Their safety and efficacy profile accounts for their extensive use. These agents may be used in monotherapy for urinary tract infections and for empiric therapy of mild to moderately severe soft tissue infections. In life-threatening infections, especially pneumonias, combination therapy is preferred to increase spectrum, to achieve synergy, and to delay the emergence of resistance. First-generation agents are frequently used in the empiric therapy of community-acquired pneumonia or sepsis when combined with an aminoglycoside. If an intraabdominal focus is strongly suspected, first-generation cephalosporins would not be appropriate but clindamycin or metronidazole are considered the antianaerobic agents with the greatest activity. In intraabdominal or pelvic sepsis, cephalosporins such as cefoxitin, cefotetan, or cefotizoxime are preferred. The second-generation cephalosporins such as cefamandole and cefuroxime have little role in the adult intensive care unit. They can be considered for infections such as sinusitis or orbital cellulitis where pathogens such as Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus may be present as a mixed infection. However, cefamandole does not penetrate the cerebrospinal fluid well and should be avoided if there is a concern of meningitis. The third-generation cephalosporins, especially those with antipseudomonal activity, have an important role in the intensive care unit, especially for empiric or definitive treatment of the more difficult infections with organisms such as Enterobacter, indole-positive Proteus, Serratia, or Pseudomonas aeruginosa. These third-generation cephalosporins should also be combined with aminoglycosides in most intensive care unit settings. The only severe infection where monotherapy would be acceptable is in the case of gram-negative meningitis. Another area where monotherapy could be considered is in the case of non-life-threatening sepsis where the concern of the nephrotoxicity associated with aminoglycoside therapy outweighs the concern over the outcome of the sepsis.

Adverse effects
The cephalosporin class of antimicrobial agents are relatively safe drugs. The incidence of all adverse effects is between 5% to 10%. However, most of these reactions are not serious or life-threatening. The most common reaction to the cephalosporins is hypersensitivity, which includes rash, fever, serum sickness, and immediate reactions.

A history of penicillin allergy frequently precludes the physician from administering a cephalosporin. This approach is not entirely justified and requires some qualification. Immunologic studies have shown cross-reactivity between patients with penicillin and cephalosporin allergy (22). Clinical data would suggest that the allergic reactions are not more frequent than 5% (23). However, immediate severe reactions to cephalosporins have occurred in at least three penicillin-allergic patients (24). Thus, though the risk of administering cephalosporins to penicillin-allergic patients is small, it would be best to avoid the use of these agents in patients with a history of anaphylaxis, bronchospasm, or urticaria after penicillin administration.

Cephalosporins have been considered as potentially nephrotoxic. However, this is true only with cephaloridine, which is no longer in use in the United States, or when cephalosporins are combined with aminoglycosides. By themselves, these agents rarely cause acute tubular necrosis or a hypersensitivity interstitial nephritis.

Other side effects, which are common but usually not serious, are gastrointestinal symptoms. These include diarrhea, nausea, vomiting, abdominal pain, and flatulence. Additionally, Clostridium difficile-associated pseudomembranous enterocolitis, though uncommon, has been reported with all of the cephalosporin antimicrobial agents. Liver enzyme elevation suggestive of hepatocellular dysfunction may also occur in approximately 3% of patients. However, clinically significant liver dysfunction secondary to cephalosporins has not been reported.

Another group of reactions has been related to the methylthiotetrazole (MTT) side chain of cephalosporins and includes cefamandole, cefoperazone, moxalactam, cefotetan, cefmenoxime, and cefmetazole. The reactions related to this structure include an alcohol-related disulfiram reaction as well as bleeding diatheses related to hypoprothrombinemia. The hypoprothrombinemia can be avoided by using lower doses of the beta-lactam containing the MTT side chain or by the concomitant administration of AquaMEPHYTON. Despite the presence of the MTT side chain, a cephalosporin will vary in its ability to cause bleeding problems. Considerably more bleeding problems have been identified with moxalactam whereas few cases have been reported with cefotetan. Other hematologic manifestations have included immune thrombocytopenia, qualitative platelet defects, and Coombs-positive hemolytic anemias.

Other side effects of the cephalosporins have included central nervous system manifestations—vertigo, hallucinations, nys-
tagmus, reversible encephalopathy, and seizures (14). These side effects are more frequent if the patient has renal failure or if the drug is given either in high doses or intrathecally.

Extended Spectrum Penicillins and Other Related Antimicrobial Agents

Penicillin is an antimicrobial agent not commonly used in the intensive care unit. However, through structural alterations of penicillin, new compounds with improved antimicrobial properties and different pharmacologic parameters have been developed. As a group, the penicillin family has a significant role in the treatment of seriously ill, hospitalized patients, especially those in the intensive care unit.

Mechanism of action

The penicillins are generally bactericidal antimicrobial agents which inhibit bacterial cell wall synthesis as described in the section on cephalosporins. The site of action is the binding of the beta-lactam to a PBP found in the plasma membrane fraction. The relative affinity for PBPs by various penicillins determines the microbiologic activity of these agents. The PBPs most important in gram-positive bacteria include PBP-1, -2, and -4. Thus, the new agents, amdinocillin and aztreonam, which do not bind these PBPs of gram-positive bacteria, are not active against these organisms. PBPs vary in their ability to bind beta-lactams as well as in their catalytic activity for peptidoglycan formation. Therefore PBPs vary in their killing potential against the bacteria and some lead only to the development of elongated or filamentous forms, whereas others lead to osmotically fragile forms with subsequent lysis. The significance of structural alterations in predicting clinical response is not known. Thus, bacterial structural alteration cannot be used as a parameter for selecting specific antimicrobial agents. However, new agents, such as amdinocillin and imipenem, which bind to PBP-2 of gram-negative organisms, may indicate an advantage of these compounds since most penicillins do not bind to the PBP-2 of gram-negative bacteria.

Spectrum of in vitro activity

Table 3 summarizes the relative activity of the penicillins (25,26). Penicillin demonstrates excellent activity against gram-positive organisms but no activity against gram-negative enteric organisms, penicillinase-producing gram-positive organisms, or penicillinase-producing Haemophilus influenzae. Penicillin is active against anaerobes except for Bacteroides fragilis and recent isolates of Bacteroides melaninogenicus. Ampicillin demonstrates similar activity to penicillin, except it is more active against Enterococcus faecalis and Haemophilus influenzae and demonstrates activity against gram-negative organisms such as Escherichia coli and Proteus mirabilis. Naficillin, a prototype penicillinase-resistant penicillin, overcomes inactivity by the beta-lactamase produced by Staphylococcus aureus. Of special note is the poor antianaerobic activity of nafcillin. The extended spectrum penicillins, azlocillin, mezlocillin, and piperacillin, have greater activity against gram-negative organisms including Enterococcus coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter, Serratia, and Pseudomonas aeruginosa. The addition of beta-lactamase inhibitors, clavulanic acid and sulbactam, enhances the activity of the penicillins against organisms.

### Table 3

Comparative In Vitro Activities of the Pencillins Against Aerobic and Anaerobic Organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Penicillin</th>
<th>Ampicillin</th>
<th>Naficillin</th>
<th>Ticarcillin</th>
<th>Ticarcillin &amp; Clavulanic Acid</th>
<th>Azlocillin</th>
<th>Mezlocillin</th>
<th>Piperacillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>+++</td>
<td>++</td>
<td>++</td>
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*Beta-lactamase strains are resistant to the indicated antimicrobial agent.
such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, and beta-lactamase-producing *Haemophilus influenzae*. This is the basis for the enhanced activity of combination agents such as ticarcillin–clavulanic acid and ampicillin–susbeptam.

### Pharmacokinetics

Intensive care unit use of the penicillins is generally confined to parenteral administration. Because of their short half-lives, nafcillin, ampicillin, and ticarcillin are administered every 4 hours. The newer extended penicillins are administered less frequently (Table 4). Penicillins are excreted via renal tubular excretion which may be blocked by probenecid, with a prolongation of serum half-lives. It is unnecessary to reduce the dose of penicillin unless there is a moderate degree of renal dysfunction (creatinine clearance < 10 mL/min), except for nafcillin, only 30% of which is excreted into the urine, the remainder inactivated in the liver (27).

Penicillins are well distributed in most body areas including the lung, kidney, bone, bile, pleura, peritoneum, and synovium. In the presence of acute inflammation, penetration is sufficiently enhanced into the cerebrospinal fluid, brain, eye, and prostate so that these agents are generally effective against susceptible organisms.

### Intensive care unit needs

Penicillin or ampicillin is the treatment of choice in the intensive care unit for infection caused by *Streptococcus pneumoniae*, *Staphylococcus pyogenes*, *Streptococcus agalactiae* (group B), *Streptococcus viridans*, *Streptococcus bovis*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Actinomyces*, and *Clostridium*. The frequency of isolating beta-lactamase-producing *Staphylococcus aureus*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae* has necessitated identification of alternate agents. *Staphylococcus aureus* can best be treated by a semisynthetic penicillin such as nafcillin, methicillin, or oxacillin. However, *Staphylococcus aureus* infections in the intensive care unit are often mixed, as is the case with pneumonia or wound infections. In such cases, another agent with a greater spectrum as well as antistaphylococcal activity may be preferred. Also, beta-lactam–resistant infections are frequent, especially at the larger referral hospitals, in burn units, or intensive care units (28). As a result, vancomycin has become a mainstay of antistaphylococcal therapy in some areas where the frequency of beta-lactam-resistant *Staphylococcus aureus* justifies this approach. The occurrence of penicillinase-producing *Haemophilus influenzae* is much less common in adults than in children, so that empiric therapy against such strains for the adult intensive care unit patient is not warranted at this time unless there is epidemiologic evidence to suggest that the problem is frequent.

The main use of penicillin for the intensive care unit is with the extended spectrum penicillins. Ticarcillin has been replaced by mezlocillin, piperacillin, and azlocillin. These agents, when combined with an aminoglycoside, often provide a synergistic antibacterial combination against most aerobic gram-negative bacilli responsible for nosocomial intensive care unit pneumonia. In addition, these agents have excellent activity against anaerobic and gram-positive organisms except for *Staphylococcus aureus*. Because of their excellent in vitro activity, the extended spectrum penicillins, when combined with aminoglycosides, can be used as empiric therapy for sepsis of most sites in the critically ill patient, unless *Staphylococcus aureus* or gram-negative meningitis is suspected.

### Adverse effects

The major side effects of the penicillins are hypersensitivity reactions. Penicillin reactions of the immediate type are of great concern. Anaphylaxis occurs in approximately four cases in 100,000 courses of penicillin administration and has been reported most frequently with penicillin (29). Delayed hypersensitivity reactions, including dermatitis, are more common with ampicillin and may occur as often as 4% to 8%.

Penicillin reactions are due to penicillin derivatives attaching to human proteins. The most important penicillin derivative is produced by opening of the beta-lactam ring, resulting in the penicilloyl derivative. Acid treatment of penicillin results in penicillanic acid. Major determinants of penicillin allergy include penicilloyl and penicillanic acid. Minor determinants are benzyl penicillin or sodium benzyl penicillin. Both major and minor determinants are associated with IgE-mediated reactions including urticaria, laryngeal edema, and anaphylaxis. Minor determinants, however, are the main cause of anaphylactic reactions. If skin testing is performed with major and minor determinants and there is failure to react to these determinants, there is a less than 5% chance of an immediate reaction occurring (30).

Gastrointestinal side effects have also occurred commonly with the penicillins, with ampicillin causing diarrhea in as many as 25% of patients. Pseudomembranous enterocolitis has also been reported with all of the penicillins.

Hematologic reactions may occur, including neutropenia and Coombs-positive hemolytic anemia. In addition, penicillin may bind to platelets resulting in a defect in platelet aggregation and rarely clinical bleeding (31).

Interstitial nephritis has been associated with high-dose penicillin administration after one week of therapy. These patients often have fever, rash, eosinophilia, albuminuria, and a rise in serum creatinine. Methicillin is the most likely penicillin to
cause interstitial nephritis (32). This immunologic complication is reversible after cessation of the penicillin, but it is inadvisable to give another penicillin during this clinical complication. Methicillin also has been reported to cause hemorrhagic cystitis.

Neurotoxicity which may occur with penicillin includes coma and seizures (33). This is most likely to occur in elderly patients with renal failure, or with intrathecal administration of the drug. Caution is necessary when adjusting the dose under these conditions. Severe hypokalemia may also be seen, with serum potassium levels of less than 2 mEq/L. This is due to kaliuresis that occurs when a large amount of nonreabsorbable anion is delivered to the distal tubule (34).

carbapenems and monobactams

A new class of beta-lactams, termed “carbapenems,” developed in recent years differ from cephalosporins and penicillins in terms of antibacterial properties. Imipenem is a prototype of the carbapenems. This agent has the greatest microbiologic activity of any agent available today (35). It is active against streptococci and staphylococci with a MIC<sub>90</sub> < 1.0 μg/mL. The enterobacteriaceae are generally susceptible to 1.0 μg/mL and Pseudomonas aeruginosa is usually susceptible to imipenem. However, Pseudomonas cepacia, Xanthomonas maltophilia, and Enterococcus faecium are usually resistant. Most anaerobes are sensitive to imipenem with a MIC<sub>90</sub> of 0.2 μg/mL for Bacteroides fragilis. The use of imipenem has been effective in many serious infections caused by susceptible organisms. Because the use of imipenem alone in the treatment of Pseudomonas aeruginosa has been associated with the emergence of resistance, aminoglycosides should be added to the therapy if possible. Imipenem has been used safely with only rare major adverse effects. Seizures have been observed as a side effect of imipenem in seriously ill patients in the intensive care unit; however, this may be no greater than the overall incidence of seizures in this patient population. The dose of imipenem is 250 to 1,000 mg every 6 hours. Dose adjustments should be made when renal insufficiency is present.

Aztreonam, a monobactam, is a monocylic beta-lactam which has excellent activity against gram-negative organisms. This agent has the advantage of lower cross-reactivity with beta-lactams in patients with a history of hypersensitivity reaction to penicillins and cephalosporins. Many Pseudomonas aeruginosa are inhibited by 25 μg/mL; however, Xanthomonas maltophilia and Pseudomonas cepacia are usually resistant (36). Additionally, monobactams do not have activity against anaerobes and gram-positive bacteria. Usual doses of aztreonam are 1 to 2 g every 8 hours.

vancomycin and teicoplanin

Use of vancomycin, a complex glycopeptide, has significantly increased throughout hospitals and especially in intensive care units. The increased usage is due not only to the increasing importance of staphylococcal infections, including both methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, but also to its continued unnecessary use when a less expensive agent can be shown to be active against the patient’s pathogen.

Mechanism of action

Vancomycin binds to the cell wall of sensitive bacteria and thus inhibits cell wall synthesis. This occurs by binding to peptide side chain ending in acyl-D-ala-D-ala of the muropeptide in the cell wall (37). Also, vancomycin inhibits the growth of spheroplasts by acting on the cytoplasmic membrane.

Spectrum of in vitro activity

Table 5 shows vancomycin’s and teicoplanin’s activity against gram-positive organisms. In addition to these gram-positive organisms, vancomycin is also active against Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus viridans, Listeria monocytogenes, clostridia (including Clostridium difficile), Bacillus anthracis, Actinomyces, lactobacilli, diphtheroids, and J-K bacillus. Although vancomycin is usually bactericidal for most gram-positive organisms, Enterococcus faecalis is usually tolerant to the antibiotic and concentrations in excess of 100 μg/mL are required to achieve a bactericidal effect.

Pharmacokinetics

Vancomycin can be given orally or intravenously. The intramuscular route of administration is not well tolerated due to severe pain. Teicoplanin, however, can be given by this route and is well tolerated. Vancomycin given orally yields undetectable serum levels even in the presence of renal failure. However, in the diseased gastrointestinal tract, such as in pseudomembranous colitis due to Clostridium difficile, serum concentrations as high as 5 μg/mL may be detected (38). Thus, vancomycin’s oral administration is limited to patients with Clostridium difficile colitis or as part of the antibacterial bowel suppression for cancer patients. When giving vancomycin intravenously, the infusion should be administered over 30 to 60 minutes to minimize untoward effects such as flushing, syncope, and arrhythmia. When 1 g of the drug is given intravenously, peak levels of 20 to 50 μg/mL and trough levels of 5 to 10 μg/mL can be achieved. Serum levels should be obtained one hour after a 60-minute infusion because of the three-stage distribution of the drug and the

Table 5

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<tr>
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<th>Vancomycin</th>
<th>Teicoplanin</th>
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<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
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<td>Staphylococcus aureus</td>
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<tr>
<td>Staphylococcus saprophyticus</td>
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MIC = minimum inhibitory concentration.
moderately variable serum results that occur in the hour after infusion.

Vancomycin achieves adequate levels in urine and pleural, pericardial, synovial, and ascitic fluids. However, in the aqueous humor, bile, and cerebrospinal fluid, levels are generally low. The level in cerebrospinal fluid tends to be greater in the presence of inflammation and in younger patients. Clinical data on the treatment of meningitis with systemic vancomycin alone have not been plentiful. Since the mean cerebrospinal fluid level achieved in adults with meningitis is 2.5 μg/mL which barely exceeds the MIC of the organism, some clinicians have chosen to administer the drug by the intrathecal or intraventricular route, via a reservoir (39).

Vancomycin has little, if any, nonrenal metabolism. It is cleared by glomerular filtration. However, a report of a patient with only hepatic dysfunction demonstrated that a prolonged half-life may occur and dose adjustments may be needed (40). The usual dosing of vancomycin is 15 mg/kg every 12 hours for adults. In the face of renal insufficiency, a daily parenteral dose of 150 mg plus 15 times the creatinine clearance can be given (41). Another approach is to give 1 g every 36 hours if the serum creatinine concentration is 1.5 to 5.0 mg/dL and 1 g every 7 to 14 days if the creatinine is > 5 mg/dL (42).

Efficacy in the intensive care unit

Vancomycin is commonly used in the intensive care unit in the treatment of serious gram-positive infections. Vancomycin is the treatment of choice for Staphylococcus aureus and Staphylococcus epidermidis infection in patients with beta-lactam (methicillin, nafcillin, oxacillin, or cephalosporin)-resistant organisms or a history of hypersensitivity to these drugs. At Henry Ford Hospital, as many as 50% of Staphylococcus epidermidis cases may be resistant to the semisynthetic penicillins and require vancomycin for therapy. Since Staphylococcus epidermidis followed by Staphylococcus aureus are frequent pathogens in device-related sepsis, the following infections are frequently treated with vancomycin: catheter sepsis, prosthetic valve endocarditis, prosthetic joints, vascular grafts, dialysis access sites, and cerebrospinal fluid shunts.

Vancomycin is also used in the treatment of enterococcal infections when the patient has a history of penicillin hypersensitivity or in the unusual case of penicillin resistance. If an endovascular infection is suspected, an aminoglycoside should be added to achieve a bactericidal regimen.

Orally administered vancomycin is the treatment of choice for pseudomembranous enterocolitis. A dose of 125 mg, four times daily, has been effective.

Teicoplanin, though used in limited amounts, has the advantage of once daily administration, as well as intramuscular administration. Currently available data are insufficient to determine its efficacy in intensive care unit-related sepsis.

Adverse effects

Although perceived by many clinicians as a highly toxic compound, the current formulation of vancomycin is relatively safe when given at a slow infusion rate. The most frequent adverse effects will occur during or shortly after administration of the drug. A histamine release results in an erythematous flushing ("red man syndrome") accompanied by pruritus or hypotension. Vancomycin should be infused over 45 to 60 minutes. Should the "red man syndrome" occur, treat with benadryl intravenously.

Nephrotoxicity, defined as a rise in serum creatinine of 0.5 mg/dL, may occur in 5% of patients receiving vancomycin alone (43). The addition of an aminoglycoside may be associated with a greater risk of nephrotoxicity than when either agent is administered alone.

Vancomycin also may be ototoxic, with hearing impairment rather than vestibular damage being the major toxicity. In general, renal insufficiency and/or excessive serum levels have been the major risk factors for ototoxicity.

Neutropenia has also been reported with vancomycin. Drug-associated neutropenia usually occurs after several weeks of therapy and is reversible over two to nine days after discontinuation of therapy. Other reported hematologic toxicities have included anemia and thrombocytopenia.

Other reported side effects of vancomycin have included phlebitis, drug fever, rash, anaphylactic reactions, and nausea.

Clindamycin, Metronidazole, and Chloramphenicol

The antimicrobial agents discussed in this section have been grouped together because of their excellent antianaerobic activity, especially against Bacteroides fragilis. Because of this activity, these agents are of considerable importance in the treatment of intraabdominal sepsis where Bacteroides fragilis is a major pathogen.

Mechanism of action

Clindamycin and chloramphenicol act by attaching to the 50S ribosomal binding sites and impairing protein synthesis. Metronidazole, on the other hand, is bactericidal by reductive activation to a compound that acts as a preferential electron acceptor which results in production of short-lived intermediate compounds or free radicals that damage DNA (44).

Spectrum of in vitro activity

Clindamycin, metronidazole, and chloramphenicol all have excellent activity against the anaerobes, especially Bacteroides fragilis. Occasional strains of Bacteroides fragilis resistant to clindamycin have been reported. Metronidazole is not active against most strains of Actinomyces and has no activity against aerobic organisms. Clindamycin, however, has the advantage of activity against Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, and Streptococcus viridans. Chloramphenicol is active not only against anaerobes but also against aerobes (except Pseudomonas aeruginosa), spirochetes, rickettsia, chlamydia, and mycoplasma.

Pharmacokinetics

Clindamycin may be given by oral, intramuscular, or intravenous routes. The dose is 300 to 900 mg every 6 to 8 hours with peak serum concentrations at one hour of 3.6 to 11 μg/mL.
Clindamycin penetrates most tissues, except for the cerebrospinal fluid. Of special interest is its higher concentration within polymorphonuclear leukocytes and macrophages.

Metronidazole can be given via oral or intravenous routes. In fact, serum concentrations for oral and intravenous routes are equivalent with peak levels, at one hour, being approximately 25 μg/mL after administering 7.5 mg/kg. The usual dosing interval is 6 to 8 hours; however, because of metronidazole's long half-life (8 hours), some investigators have given this drug as infrequently as once a day. Clinical experience with this dose schedule is limited. Metronidazole penetrates all tissues well, including cerebrospinal fluid, brain, and other abscesses.

Chloramphenicol may be given by oral, intramuscular, or intravenous routes. An unusual observation is that serum concentration with the oral route is higher than with parenteral routes of administration (45). This is due to incomplete hydrolysis by the liver of the intravenous preparation, chloramphenicol succinate, with resultant serum concentration of only 70% of those obtained after oral administration. Although tolerated well, the intramuscular route of administration is not recommended because of a high relapse rate related to low serum levels due to poor absorption of the ester from the injection site. Chloramphenicol penetrates most tissues achieving cerebrospinal fluid levels that are 30% to 50% of the serum concentration. Like metronidazole and clindamycin, chloramphenicol is metabolized primarily in the liver; thus, in renal failure, dose alterations are not needed.

**Efficacy in the intensive care unit**

Clindamycin may be used for infections outside of the central nervous system where *Bacteroides fragilis* or other penicillin-resistant anaerobic bacteria are suspected. Thus, in intraabdominal sepsis and in anaerobic pleural-pulmonary infection, clindamycin, when combined with an aminoglycoside, has become a first-line therapy. Previous recommendations for anaerobic pulmonary infections have emphasized penicillin; however, a recent study of putrid lung abscess showed clindamycin to be more effective than penicillin (46).

Another area for clindamycin is in the patient with penicillin allergy who has a methicillin-sensitive *Staphylococcus aureus* or a penicillin-sensitive anaerobic infection such as *Clostridium perfringens*.

Metronidazole can be used in intraabdominal sepsis but must be combined with an agent effective against aerobic gram-negative organisms. In such cases, metronidazole is considerably more cost-effective than clindamycin. In addition, metronidazole is active against *Bacteroides fragilis* resistant to clindamycin. In pulmonary infections, metronidazole has been associated with an unacceptable failure rate and must always be combined with a second agent, such as a beta-lactam antibiotic active against aerobes found in the oral cavity.

Metronidazole has become a preferred agent in the treatment of anaerobic central nervous system infections. In anaerobic infections at any site, clinical failure may occur with metronidazole if *Actinomyces* are encountered.

Chloramphenicol is seldom used for anaerobic infection in view of the efficacy and safety profiles of clindamycin and metronidazole. Intensive care use of chloramphenicol is limited to unusual infections such as salmonella resistant to ampicillin and sulfamethoxazole/trimethoprim, penicillin-allergic patients with pneumococcal or meningococcal meningitis, and rickettsial infections such as Rocky Mountain spotted fever and typhus.

**Adverse effects**

Side effects of clindamycin include rash, fever, anaphylaxis, hepatotoxicity, reversible neutropenia, thrombocytopenia, and leukopenia. Gastrointestinal side effects are the most common, with up to 20% of patients having diarrhea and 0.01% to 10% developing pseudomembranous enterocolitis. In the case of clindamycin-associated enterocolitis, diagnosis should be made by demonstrating toxin in the stool. If suspected, the offending antimicrobial should be discontinued and vancomycin administered orally in doses of 125 to 500 mg every 6 hours.

Metronidazole is generally well tolerated with few serious side effects. Neurologic side effects have included seizures, ataxia, neuropathy, and encephalopathy. Other reactions have included potentiation of coumadin, metallic taste, gastrointestinal disturbances, urticaria, and reversible neutropenia.

The major toxicity of chloramphenicol that has limited its clinical use has been concern over the idiosyncratic reaction of aplastic anemia which occurs only in one of 25,000 to 40,000 patients who receive the drug. Other side effects include reversible dose-related bone marrow depression manifested by reticulocytopenia, anemia, leukopenia, and thrombocytopenia, as well as optic neuritis, gray baby syndrome, hypersensitivity reaction, gastrointestinal symptoms, rash, and drug fever.

**Sulfamethoxazole/Trimethoprim**

Sulfamethoxazole/trimethoprim is used with increasing frequency in the intensive care unit. The main indications have been *Pneumocystis carinii*, nocardia infection, gram-negative infection where *Pseudomonas aeruginosa* is not suspected, and methicillin-resistant *Staphylococcus aureus* (47). The drug may be given in doses of 7 to 20 mg/kg/day of trimethoprim in two to four divided doses. In the case of *Pneumocystis carinii* pneumonia, the higher dosage recommendation should be given. The drug penetrates most body tissues including the central nervous system. Side effects include nausea, vomiting, diarrhea, hyper-sensitivity reactions, leukopenia, thrombocytopenia, and renal dysfunction. In addition, sulfamethoxazole/trimethoprim may interfere with some of the methods to determine serum creatinine, giving a false elevation.

**Erythromycin**

Erythromycin has also increased in usage in the intensive care unit, especially for the treatment of *Legionella* species, *Mycoplasma pneumoniae*, diphtheria, pertussis, chlamydia, and *Campylobacter* infections. When given intravenously, the dose is 500 to 1,000 mg every 6 hours. Side effects include phlebitis, nausea, vomiting, diarrhea, pseudomembranous enterocolitis, sensorineural hearing loss, fever, rash, eosinophilia, and hepatotoxicity.
Quinolones

The quinolone group of antimicrobial agents appears to be highly effective against the enterobacteriaceae. The available quinolones, ciprofloxacin, ofloxacin, and norfloxacin, have poor activity against streptococci and anaerobes. Ciprofloxacin has marginal activity against Staphylococcus aureus and Pseudomonas aeruginosa with the emergence of resistance to these pathogens becoming commonplace.

To date, ciprofloxacin is the only available parenteral quinolone. The dose recommended is 400 mg intravenously every 12 hours. It is important to keep in mind the problem of drug interactions. In the intensive care unit the major drug of concern would be theophylline which will have decreased excretion in the presence of ciprofloxacin therapy. Theophylline levels should be monitored and dose adjustments made accordingly to avoid theophylline toxicity.

The most important role for parenteral ciprofloxacin in the intensive care unit will be for Pseudomonas aeruginosa and other gram-negative organisms resistant to beta-lactams and/or aminoglycosides. In addition, the quinolones have good in vitro activity against atypical pneumonia pathogens including Legionella pneumophila and Chlamydia pneumoniae.

Antifungal Therapy

Antifungal therapy in the intensive care unit is usually limited to parenteral agents, specifically amphotericin B which is used in the therapy of candidiasis, cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis, aspergillosis, mucormycosis, and visceral sporotrichosis. Therapy should be initiated with a 1 mg test dose over 1 to 2 hours to assess the patient’s febrile and cardiopulmonary response. The dose may then be increased to 0.3 mg/kg/day which should be given over 4 to 6 hours. Over three to five days, the dose may be increased to 0.6 mg/kg/day. Infusion reactions may be reduced by the administration of benadryl, antipyretics, heparin (1,000 units), and hydrocortisone (50 to 100 mg). Side effects that may necessitate reduction or temporary discontinuance of therapy include azotemia, anaphylaxis, fever, rigors, hypokalemia, anemia, thrombocytopenia, and leukopenia. 5-Flucytosine should be combined with amphotericin in treating cryptococcal disease, and serum levels should be carefully monitored to avoid bone marrow suppression.

The antifungal fluconazole is available in parenteral and oral forms. In the intensive care unit this agent could be used as a second-line therapy in cryptococcal meningitis for the patient who cannot be treated with amphotericin or as maintenance therapy after a successful induction with amphotericin. The use of fluconazole in disseminated candidiasis has not been sufficiently studied to recommend its use over amphotericin at this time.

Acyclovir

Acyclovir is the antiviral agent of greatest value to the intensive care patient. This purine nucleoside analogue can be used for herpes simplex encephalitis, disseminated herpes simplex infection, localized varicella zoster in immunocompromised patients, and disseminated varicella infection. The dose of acyclovir is 5 to 10 mg/kg every 8 hours, with the higher dose being used for herpes encephalitis, disseminated or localized varicella zoster, and disseminated herpes simplex infection. The toxicity of acyclovir is minimal with less than 1% of patients developing serious side effects. Reported side effects include headache, nausea, rash, hypotension, lethargy, obtundation, seizures, or coma. Renal dysfunction may occur if the patient is dehydrated, and crystalluria is a concern as well. Thus, adequate hydration is critical when administering acyclovir.

References