Current Use for Old Antibacterial Agents: Polymyxins, Rifamycins, and Aminoglycosides

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The polymyxins, rifamycins, and the aminoglycosides may be considered special use antibacterial agents. They are all old agents and are rarely considered the drugs of choice for common bacterial infections.

The polymyxins are increasingly important because of the continued emergence of multidrug resistant (MDR) gram-negative organisms, such as strains of *Pseudomonas aeruginosa* or carbapenemase-producing Enterobacteriaceae that are susceptible to few remaining drugs. Rifampin is only considered in the context of nonmycobacterial infections where its role is limited and sometimes controversial. Rifaximin is a new enteric rifamycin that is increasingly used for gastrointestinal infections such as traveler’s diarrhea and *Clostridium difficile* infections (CDIs). This article will also review the current role of aminoglycosides in nonmycobacterial systemic infections, with an emphasis on the use of single daily administration.

POLYMYXINS

The polymyxins were discovered in 1947. Although there are five known polymyxin molecules, sequentially named polymyxin A through polymyxin E, only two polymyxins are available for therapeutic use: polymyxin B and polymyxin E (colistin) (Table 1). Both polymyxin B and polymyxin E are large cyclic cationic polypeptide detergents

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with molecular weights of 1000 or more. Polymyxin B was initially isolated from *Bacillus polymyxa*, and colistin was isolated from *Bacillus colistinus*. There are two preparations of colistin: colistin sulfate and colistimethate sodium. Colistimethate sodium is inactive until hydrolyzed and such hydrolysis occurs in both in vivo and in vitro testing systems. Notably, colistimethate sodium is the least active polymyxin in vitro (as much as fourfold to eightfold less active)\(^1\) but also is the least nephrotoxic compound compared with polymyxin B and colistin sulfate.\(^2,3\)

The polymyxins were used to treat serious infections caused by gram-negative bacilli in the early 1960s until aminoglycosides active against *P. aeruginosa* (eg, gentamicin) came into common use. The polymyxins fell into further disuse by 1980 because of their nephrotoxicity and subsequently they became mainly reserved for topical and oral administration.\(^4,5\) The recent emergence of *P. aeruginosa*, *Acinetobacter baumannii*, and MDR gram-negative bacilli resistant to all other antimicrobial agents has resulted in the increasing need for an injectable polymyxin.\(^6,7\)

In recent years, colistimethate sodium has been the most commonly used form of polymyxin for parenteral therapy. Colistimethate has also been used for nebulization therapy in patients with cystic fibrosis and for intrathecal and intraventricular injection. Colistin, on the other hand, has been available as colistin sulfate for use topically and orally, except in the United States, where only colistimethate and polymyxin B are available commercially.

Polymyxin B sulfate can be given intramuscularly and intravenously and is available for topical use. Polymyxin B has also been used intrathecally and intraventricularly for central nervous system infections.

### Mechanism of Action and Antimicrobial Activity

The polymyxins act on the cell wall of gram-negative bacteria by way of three known mechanisms of action. (1) Polymyxins are cationic molecules that electrostatically disrupt bacterial surface membranes by displacing Ca\(^{2+}\) and Mg\(^{2+}\) ions that stabilize lipopolysaccharide (LPS) molecules. (2) Polymyxins are surface-active amphipathic agents containing both lipophilic and lipophobic groups. They penetrate into cell membranes and interact with phospholipids in the membranes, leading to permeability changes that quickly disrupt cell membranes leading to cell death.\(^8\) (3) Polymyxins also bind to the lipid A portion of endotoxin or LPS molecules and, in animal studies, block many of the biologic effects of endotoxins.\(^9\)

The polymyxins are active against commonly isolated gram-negative aerobic bacilli with the exception of *Proteus* spp, which are generally very resistant to the polymyxins. In addition, the polymyxins have poor activity against *Serratia, Providencia, Burkholderia, Vibrio, Brucella, Helicobacter, Moraxella, Aeromonas, Morganella*, and *Edwardsiella*.\(^5,10\) Fortunately, the polymyxins have retained activity against many drug-resistant gram-negative bacilli, such as *P. aeruginosa* and *A. baumannii*. When

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tested against colistin sulfate, most gram-negative bacilli are inhibited by 1.0 \( \mu \text{g/mL} \); \( P \) aeruginosa strains are more resistant, but most strains are inhibited by 2.0 \( \mu \text{g/mL} \).\(^{10}\) \( Pseudomonas \) strains with a minimal inhibitory concentration (MIC) greater than 4.0 \( \mu \text{g/mL} \) and \( Acinetobacter \) strains with a colistin MIC of greater than 2 mcg/ml are defined as resistant.\(^{11}\)

Polymyxins are not active against gram-positive organisms and most anaerobes. Fortunately, resistance of gram-negative bacteria to the polymyxins remains uncommon\(^{12–14}\); however, heteroresistance has been reported in isolates of \( Acinetobacter \).\(^{15,16}\) When resistance is present however, there is complete cross-resistance between the polymyxins.\(^{17}\) Such resistance of gram-negative bacteria to the polymyxins is usually related to changes in the architecture of LPS molecules in the cell wall that interfere with the interaction between peptides of the polymyxin (which are positively charged) and the LPS molecules (which are negatively charged).\(^5\) The PmrA-PmrB and PhoP-PhoQ systems regulate the charge of Lipid A and LPS in gram-negative bacteria and appear to have important roles in this mechanism of resistance.\(^{18,19}\) Studies have shown less common mechanisms of resistance to polymyxins. For example, one study of colistin-resistant \( Pseudomonas \) isolates revealed alterations in bacterial cell membrane, including reduced density of LPS molecules, and reduced concentration of \( \text{Ca}^{2+} \) and \( \text{Mg}^{2+} \) ions.\(^1\) Interestingly, the emergence of polymyxin-resistant \( P \) aeruginosa has been linked to the use of nebulized colistimethate in patients who have cystic fibrosis.\(^{2,20}\) Another recent report showed that efflux pump/potassium channels may mediate resistance in isolates of polymyxin-resistant \( Yersinia \) spp.\(^{21}\) The activity of the polymyxins is diminished in the presence of high concentrations of divalent cations such as calcium and magnesium.\(^1\)

**Pharmacokinetics**

The basic and clinical evaluation of the polymyxins took place many years ago, and reliable pharmacokinetic data are lacking. Furthermore, review articles often do not differentiate forms of polymyxin and often have internally inconsistent data concerning pharmacokinetics, especially blood levels.\(^22\)

When administered orally, none of the polymyxins are absorbed. According to old literature, following intramuscular injection of 2–4 mg/kg polymyxin B, peak serum levels of 1–8 \( \mu \text{g/mL} \) were achieved. There is little reliable data on serum levels after IV administration of polymyxin B. A very recent study using 0.5–1.25 mg/kg polymyxin B, given by IV infusions over an hour to critically ill subjects, reported peak plasma concentrations of 2.4–14 \( \mu \text{g/mL} \) drawn after at least 2 days of therapy. Serum protein binding was 79%–92%.\(^{23}\)

When colistimethate was given intramuscularly to adults at a dose of 2.5 mg/kg, a peak serum level of 5–7 \( \mu \text{g/mL} \) was achieved. In old reports, the peak serum level following intravenous administration of colistimethate was about 20 \( \mu \text{g/mL} \). The package insert for colistimethate shows peak levels of about 8 \( \mu \text{g/mL} \) and 20 \( \mu \text{g/mL} \), respectively, following intramuscular and intravenous administration of 150 mg.

In very limited studies, however, following 2 to 3 mg/kg intravenous administration of colistimethate, the peak level of colistin, the active metabolite was only about 2 \( \mu \text{g/ml} \) (which is much lower than the peak of colistimethate).\(^{24}\) Because serum protein binding of colistin is about 50%, the peak antibacterial activity in serum of active colistin following administration of recommended doses is borderline at best.\(^{24}\) Finally, in a recent pharmacokinetic analysis, steady state concentrations of 2.3 mcg/mL were achievable when colistimethate was administered at 240 mg every 8 hours.\(^{25}\)
According to past literature, the excretion of polymyxin B and colistin is primarily by glomerular filtration. After the initial dose of polymyxin B (but not colistimethate) there is a 12- to 24-hour lag before significant amounts of drug are found in the urine. After administration of subsequent doses, the urine levels of both polymyxin B and colistimethate exceed 15 μg/mL for at least 6 hours. In a recent study, less than 1% of infused polymyxin B was recovered unchanged in the urine.23

The half-life of polymyxin B in serum is about 4.5 to 6 hours.26 There is relatively little information available on the serum half-life of colistin (the active antibiotic) following injection of colistimethate. In subjects who have cystic fibrosis, the serum half-lives of colistimethate and colistin were 2 hours and 4 hours, respectively.24 Half-lives of these agents are prolonged when given to patients who have renal insufficiency or are critically ill.27 Distribution to the cerebrospinal fluid (CSF), biliary tract, pleural fluid, and joint fluid is poor.28 However, in one report, the peak CSF levels following the intravenous administration of colistimethate were 25% of the peak serum levels.29

Serum levels of the polymyxins are very low following inhalation therapy.30 The polymyxins are poorly dialyzed and there is minimal hepatic metabolism or biliary excretion.

**Pharmacodynamics**

Polymyxin B and colistin have rapid bactericidal effect in vitro in a concentration-dependent manner. There is well-described postantibiotic effect (PAE) for *P. aeruginosa* with delayed regrowth, as compared with rapid regrowth of MDR *A. baumannii* with no PAE because of heteroresistance.5,31 Because of the potential lack of PAE, three times a day dosing has been suggested by in vitro studies.32 It has also been suggested that the polymyxins be used in combination with another active drug if there is one. Studies of in vitro synergy have been limited to relatively few organisms. Using colistin-susceptible strains of MDR bacteria, synergism has been demonstrated between a polymyxin and ceftazidime, rifampin, trimethoprim-sulfamethoxazole, imipenem, cefepime, tigecycline, and azithromycin.33–40

**Toxicity**

Dose-related nephrotoxicity is the most common and the most important adverse effect associated with polymyxins.41 The nephrotoxicity is attributed to direct damage of the cells in the distal convoluted tubules,42 and is usually reversible after the drug is discontinued.22,43 Early literature suggested that 10%–30% of subjects who received polymyxins developed reversible renal impairment. However, more recent reports indicate that the nephrotoxicity with polymyxins may be less than aminoglycosides.15 In addition, studies that adjusted for severity of illness and pre-existing renal impairment have found that subjects receiving colistimethate experienced similar rates of nephrotoxicity compared with cohorts receiving carbapenems and other agents for infections caused by *P. aeruginosa* and *A. baumannii*.7,44,45 Nephrotic effects are enhanced, however, when the polymyxins are used in subjects receiving other nephrotoxic agents.46

Dose-related neurotoxicity occurs in approximately 5% of subjects receiving polymyxins, according to more recent literature. There are several manifestations of neurotoxicity: (1) Neuromuscular blockade, which can involve the respiratory musculature and cause apnea and can be potentiated by aminoglycosides4,22; (2) Sensory disturbance with perioral paresthesias, paresthesias of the tongue, and paresthesias of the extremities; and (3) Polyneuropathy, including cranial nerve palsies (diplopia, nystagmus).
Neuromuscular blockade is most likely to occur when the drug is used in excessive doses in patients who have renal failure, or in those who are receiving curariform drugs. When respiratory paralysis occurs, it is necessary to support respiratory function until the effects of the drug wear off. Intravenous calcium may help reverse the respiratory paralysis. Aminoglycosides may potentiate the neurotoxic effects. Other neurotoxic side effects, such as perioral paresthesias, parathesias of the tongue and extremities, and peripheral neuropathy are not uncommon. Toxicity is less likely to occur with colistimethate than with polymyxin B.

Hypersensitivity to polymyxins is unusual, but up to 2% of patients receiving parenteral polymyxins can develop allergic manifestations, including fever, eosinophilia, and rashes.

In general, toxicity is less likely to occur with colistimethate than with polymyxin B. Intraventricular and intrathecal administration of the polymyxins are generally well tolerated. Nebulization may result in bronchoconstriction. A warning has been issued by the FDA against premixing colistimethate too far in advance of nebulization because of one possible drug-related death.

Clinical Indications

In the United States, polymyxin B and colistimethate are approved only for use intravenously (which is preferred) and intramuscularly. However, aerosols and the intrathecal and intraventricular routes have become relatively common. Polymyxin B is very painful when given intramuscularly, and this route of administration should be avoided. The dosage of polymyxins below are expressed in terms of the polymyxin base. If IM injection is necessary, the usual IM dose is 2.5–3 mg/kg/day in divided doses every 4 to 6 hours. The IV dose is 1.5–2.5 mg/kg/day by continuous IV infusion or in divided doses every 12 hours over a period of 60 to 90 minutes.

For treatment of gram-negative bacillary central nervous system infection, the Infectious Diseases Society of America guidelines recommend a daily dose of 5 mg polymyxin B intraventricularly. Polymyxin B has been given intrathecally in doses of 5–10 mg/day for the initial 3 days of therapy and then every other day until cultures are negative.

The recommended dosage of colistimethate in adults who have normal renal function is 2.5–5 mg/kg (depending on the severity of infection) each day intramuscularly or intravenously in two to four divided doses. The dose should be based on ideal body weight and should not exceed 300 mg/day. Doses must be decreased in patients who have impaired renal function to avoid drug accumulation and toxicity. When given intravenously, colistimethate is administered over 3 to 5 minutes. Administration of doses as high as 8 mg/kg/day has been reported recently. The question has been raised about the use of colistimethate as a single daily dose to theoretically lower the risk of toxicity, but clinical validation is lacking and, for reasons stated above, is not a good idea.

For treatment of central nervous system infection, the Infectious Diseases Society of America guidelines suggest an intraventricular dose of 10 mg of colistimethate. The same dose would presumably be used intrathecally.

Colistin sulfate has been used orally for intestinal decontamination. The oral preparation is not available in the United States.

Inhalation therapy with aerosolized colistimethate has been used with varying success to treat colonization or infection of the bronchial system, especially with MDR P aeruginosa, in patients who have cystic fibrosis. Systemic blood levels are not achieved with inhalation therapy. The usual dose in adults is 80 mg every 12 hours. Up to 160 mg every 8 hours has been used.
Most of the literature on the use of the polymyxins for parenteral therapy is old. In recent years, colistimethate has been used parenterally to treat systemic infections caused by MDR gram-negative bacilli, mainly ventilator-associated pneumonia. In contrast with past experience, recent reports claim little in the way of nephrotoxicity or neurotoxicity. However, more modern-day experience is necessary before colistimethate can be considered a relatively nontoxic systemic agent. Reports of use of polymyxin B in modern medicine have been sparse.

Recent observations have indicated that emergence of polymyxin resistance in *P. aeruginosa, K. pneumoniae,* and *A. baumannii* is associated with the use of this class of agents. Until more clinical data become available, parenteral polymyxin B and colistimethate should be reserved for use only when no other less toxic or potentially more effective drug can be used.

**RIFAMPIN AND RIFAXIMIN**

Rifamycins are a group of broad-spectrum antibiotics that interfere with bacterial DNA-dependent RNA polymerase and are active against mycobacteria and various gram-positive and gram-negative organisms. This section focuses on the use of rifampin against nonmycobacterial organisms, and is followed by a discussion of rifaximin, a novel rifamycin derivative that is increasingly used as an enteric antibiotic against traveler’s diarrhea and is being evaluated for *Clostridium difficile* infections (CDIs).

**Rifampin**

Rifampin, or rifampicin, the prototypical rifamycin, was first synthesized in 1965 from a fermentation product of *Streptomyces mediterranei.* It kills proliferating extracellular organisms, intracellular mycobacteria, and semidormant subpopulations of mycobacteria that reside in tissues.

Although rifampin is best known for its antimycobacterial activity, the drug is highly active against both coagulase-positive and -negative staphylococci and other gram-positive cocci, such as *S. pyogenes* and *S. pneumoniae.* Enterococci are only moderately susceptible. Among gram-negative organisms, *N. meningitidis,* *N. gonorrhoeae,* and *H. influenzae* are the most susceptible.

In addition to its broad spectrum of activity, rifampin has interesting pharmacokinetic properties and has the unusual ability to enter cells and mediate antibacterial activity at intracellular sites.

**Mechanism of action and antimicrobial activity**

Rifampin acts by inhibiting DNA-dependent RNA polymerase after binding to the beta subunit of the enzyme. This interaction interferes with protein synthesis by preventing chain initiation. Rifampin is usually bactericidal, but may be bacteriostatic depending on the organism and the drug concentration. Hence, rifampin demonstrates concentration-dependent killing and has a very long PAE. Those organisms inhibited by 1.0 μg/mL or less are considered to be susceptible to rifampin, those inhibited by 2.0 μg/mL are intermediate, and those with a MIC of 4.0 μg/mL or more are resistant.

Most gram-positive cocci (staphylococci and streptococci) are highly susceptible to rifampin (MICs <1 μg/mL); enterococci, which are only moderately sensitive, are an important exception.

Meningococci, gonococci, and *H. influenzae* are susceptible to rifampin. In contrast, most gram-negative bacilli are intrinsically resistant to rifampin.
Acquired resistance to rifampin occurs rapidly when it is inappropriately used as monotherapy and often develops by mutations in the gene \(\text{rpoB}\) encoding the beta subunit of DNA-dependent RNA polymerase. Additionally, resistance can be mediated by alterations in membrane permeability.\(^6\)

The effects of combining rifampin with other antibiotics remain a confusing area due to conflicting in vitro and in vivo data. When rifampin is added to other bactericidal agents, the effect may be synergistic, additive, indifferent, or antagonistic depending on the drugs, their concentrations, the organisms being studied, and the model. Examples of some of the results follow.

Addition of rifampin to penicillinase-resistant penicillins in vitro inhibited the bactericidal activity of the penicillins against \(\text{S. aureus}\).\(^6\) In a rabbit model of \(\text{S. aureus}\) endocarditis, the combination of a penicillinase-resistant penicillin and rifampin was synergistic for some strains and indifferent or antagonistic for other strains.\(^5\) The addition of rifampin to vancomycin or to vancomycin-plus-gentamicin improved the effectiveness of therapy in a rabbit model of \(\text{Staphylococcus epidermidis}\) endocarditis.\(^6\) Similarly, substantial improvements in cure rates for \(\text{S. epidermidis}\) prosthetic valve endocarditis were achieved by adding rifampin, gentamicin, or both, to vancomycin.\(^6\)

Experimental meningitis studies with limited number of strains of pneumococci have demonstrated that addition of rifampin to vancomycin or ceftriaxone may have differing effects on the rate of killing of pneumococci in CSF. One study showed a beneficial effect.\(^6\) In contrast, another study demonstrated no increase in killing rate against pneumococci when rifampin was added to vancomycin.\(^7\) Interestingly, an in vitro study showed that the addition of rifampin to ceftriaxone resulted in a marked decrease in killing rates of ceftriaxone-susceptible pneumococci, compared with ceftriaxone alone.\(^7\)

Synergism has been demonstrated between colistin and rifampin in vitro and in vivo against certain MDR strains of bacteria.\(^3\)\(^4\)\(^3\)\(^6\)\(^8\)

**Pharmacokinetics**

Rifampin is well absorbed when given orally with peak serum concentrations of 7 to 10 \(\mu\)g/mL following a dose of 600 mg. Food interferes with enteric absorption and rifampin should therefore be administered on an empty stomach. An intravenous preparation is available when the oral route cannot be used. Dosing is identical for the oral and intravenous preparations.

Rifampin is widely distributed into tissues and different compartments despite being 80% protein-bound. It penetrates well into body fluids, achieving therapeutic levels in saliva, bile, bone, pleural fluid, prostate, and CSF. Moreover, rifampin readily enters phagocytic cells and can kill microorganisms in the cells.

Rifampin undergoes a multistep process of elimination. It is first de-acetylated in the liver and then cleared by hepatic metabolism and biliary excretion. The half-life of rifampin is 2 to 5 hours, which can be prolonged by hepatic disease and shortened by repeated dosing due to rifampin’s propensity to induce its own metabolism by way of the P450 enzymes. Rifampin does not need dose-adjustment in the setting of renal insufficiency.

**Toxicity**

With administration of rifampin, urine and sweat often develop an orange tinge and soft contact lenses may be stained. This adverse effect of discoloring body fluids is almost universal and may be used as a surrogate marker of adherence. A flulike syndrome can occur in up to 5% of patients who have had prolonged intermittent
use of rifampin. Rash and gastrointestinal adverse effects (eg, nausea, vomiting, diarrhea, heartburn) may occur in up to 5% of patients. Abnormal liver function tests are common but frank hepatitis is uncommon (<1%), especially with short courses used for nonmycobacterial infections.

The potential for rifampin to induce hepatic microsomal enzymes can cause multiple drug–drug interactions; such interactions can occur with oral contraceptives, cyclosporine, digoxin, fluconazole, sulfonylureas, theophylline, thyroxine, warfarin, antipsychotics and antiretroviral agents.

**Clinical indications**

Rifampin should always be coupled with another bacterioactive agent and should never be used as monotherapy, except when used for chemoprophylaxis of meningococcal and *H influenzae* infections. The course of chemoprophylaxis is always short and is designed to eradicate the organism from the nasopharynx. Furthermore, rifampin is now seldom used to prevent *H influenzae* infections because of decreased rates of the infection due to widespread use of the *H influenzae* vaccine.

Rifampin is administered in a dose of 10 mg/kg (not to exceed 600 mg) in patients at least 1 month of age, twice a day for 2 days for prevention of meningococcal disease; this generally has had an efficacy of more than 90%. However, rifampin has several shortcomings, including nasopharyngeal eradication rates of only about 70%–80% in some studies, adverse effects, and the necessity for multiple doses over 2 days. Moreover, resistance to rifampin in isolates of *N meningitidis* in the United States is increasingly detected (up to 10%–27% of *N meningitidis* isolates). Ciprofloxacin may be more effective in eradicating meningococci. To protect children under 4 years of age who have been incompletely immunized against *H influenzae* type B, all household contacts who have been in contact with a case of severe infection should receive rifampin prophylaxis. The dose in adults is 600 mg twice daily for 2 days.

Rifampin has been used in combination with other nonmycobacterial agents in some limited situations, including (1) Staphylococcal infections, especially on foreign bodies (eg, prosthetic valve endocarditis); (2) Pneumococcal meningitis in which corticosteroids are being given in addition to vancomycin and a third generation cephalosporin; and (3) As combination therapy for certain zoonoses, such as Brucellosis, Q fever, Bartonellosis and Rhodococcus infections.

**Staphylococcal infection** In an attempt to achieve higher rates of cure, rifampin has been increasingly used by some in combination with standard antistaphylococcal therapy for severe infections caused by staphylococci. Rifampin has several properties that are theoretically advantageous in the treatment of complicated staphylococcal infections: (1) Rifampin is bactericidal against *S aureus*, (2) Rifampin achieves high intracellular levels, and (3) Rifampin can penetrate biofilms.

Even though rifampin has these desirable characteristics, data to support the practice of combining rifampin and another antistaphylococcal agent are limited and are typically based on small clinical studies or animal and in vitro investigations. A recent meta-analysis concluded that many animal studies showed a microbiologic benefit of adjunctive rifampin use, particularly in osteomyelitis and infected foreign body infection models. Few human studies have adequately addressed the role of adjunctive rifampin therapy. Adjunctive therapy seems most promising for the treatment of osteomyelitis and prosthetic device-related infections, although studies typically have been underpowered and benefits were not always seen.

A substantial improvement in cure rates for *S epidermidis* prosthetic valve endocarditis was reported in a noncontrolled study by adding rifampin, gentamicin, or both, to
vancomycin. As a result of this study and in vitro and animal studies, the American Heart Association recommends the addition of 300 mg rifampin orally every 8 hours for treatment of \textit{S epidermidis} prosthetic valve endocarditis.

Because of the excellent penetration of rifampin into tissues and organ spaces, there is a general enthusiasm for including rifampin in regimens when treating staphylococcal infections in the presence of abscesses or foreign bodies.

Despite the benefit of adding rifampin to the regimen in animal models of \textit{S aureus} osteomyelitis, clinical studies have not been convincing. However, in the presence of a foreign body, it is reasonable to add rifampin.

Rifampin alone or in combination with another drug (eg, trimethoprim-sulfamethoxazole) has been used to eradicate nasal carriage of \textit{S aureus}, including methicillin-resistant strains (MRSA). These combinations have also been used for oral treatment of non–life-threatening MRSA infections.

\textbf{Pneumococcal meningitis} Despite high in vitro susceptibility against \textit{S pneumoniae}, rifampin should never be used alone to treat pneumococcal meningitis. When the infecting organism is highly resistant to ceftriaxone and cefotaxime but is rifampin-susceptible, combination therapy with vancomycin plus ceftriaxone plus rifampin might be effective. In these circumstances, vancomycin concentrations should be maximized to ensure adequate CNS penetration. Steroid therapy can reduce antimicrobial penetration into CSF by decreasing inflammation; in animal models, steroid therapy has been associated with failure of cephalosporin or vancomycin monotherapy, although this has not been observed in all experimental studies. For these reasons the Infectious Disease Society of America recommends addition of rifampin to the vancomycin, third generation cephalosporin, and dexamethasone regimen used for pneumococcal meningitis.

Despite these recommendations, there are no reliable clinical data concerning results of the addition of rifampin to vancomycin and/or a third-generation cephalosporin in subjects who have pneumococcal meningitis. Because there are conflicting results of the benefits of rifampin in animal model and in vitro studies, it has been suggested that rifampin be used for patients in whom the pneumococcal isolate is sensitive to rifampin in vitro and who are not responding appropriately to standard therapy.

\textbf{Brucellosis} Rifampin in combination with doxycycline plus and minus an aminoglycoside has been shown to have better cure rates for brucellosis than other antibiotic combinations in recent meta-analyses.

\textbf{Rifaximin}

Rifaximin is a new enteric antibiotic that is only available as an oral preparation. Like other rifamycins, rifaximin binds the beta subunit of the DNA-dependent RNA polymerase, and inhibits RNA synthesis. Unlike rifampicin, however, rifaximin acts exclusively in the gastrointestinal tract and is poorly absorbed due to the presence of a pyridoimidazole moiety.

\textbf{Spectrum of activity}

Rifaximin is active against most gram-positive organisms, including \textit{C difficile} and essentially all enteric gram-negative pathogens, including \textit{E coli}, \textit{H pylori}, \textit{Y enterocolitica}, and \textit{Shigella} spp.

Despite its broad antibiotic spectrum, rifaximin appears to have little impact on normal gastrointestinal flora. In one study, there was an initial decrease in the gastrointestinal flora following rifaximin administration, followed by rapid normalization of
enteric flora within the month. Development of resistance to rifaximin appears to occur with low frequency.

**Adverse effects**
Rifaximin is generally well tolerated, with similar rates of adverse effects in subjects receiving comparator drugs and placebos. Headache was more common in one study. Rifaximin is not expected to have drug–drug interactions via the CYP 450 system because it is not systemically absorbed.

**Clinical indications**
Rifaximin is currently approved for the treatment of traveler’s diarrhea caused by noninvasive strains of *E coli*. Three studies showed rifaximin to be effective in shortening the duration of diarrhea. The approved dosage is 200 mg three times per day for 3 days.

Rifaximin is also being considered in the therapy for *C difficile* infections. One study in the hamster model showed oral rifaximin to be as effective, if not more effective, than oral vancomycin for two standard strains of *C difficile*. Several treatment strategies with rifaximin have shown positive outcomes in refractory *C difficile* infections, including combination therapy of vancomycin and rifaximin, and even a strategy of sequential monotherapy of vancomycin and rifaximin.

In one small case series, eight subjects who had recurrent symptoms of *C difficile* infection received sequential therapy of oral vancomycin and then rifaximin. At the end of the study, all but one subject remained symptom free. Unfortunately, the study also reported that the rifaximin MIC for *C difficile* isolates recovered after therapy (>256 μg/mL) was much higher than the MIC for isolates recovered before therapy (0.0078 μg/mL). The use of rifaximin for *C difficile* infections remains off-label and caution should be exercised because drug resistance was clearly demonstrated after rifaximin use in the study.

**AMINOGLYCOSIDES**
The aminoglycosides are a class of bactericidal antibiotics characterized by the presence of a six-carbon aminocyclitol ring, covalently bonded to multiple amino sugar groups. Aminoglycosides were once widely used as primary agents in the therapy of gram-negative bacillary infections. However, because of their toxicity and the availability of newer effective agents, systemic aminoglycosides have been primarily relegated to a role as companion drugs either to broaden coverage against gram-negative aerobic bacilli or to provide synergistic killing against gram-positive cocci or certain gram-negative bacilli. Now, because of the emergence of MDR gram-negative bacilli, the aminoglycosides, along with the polymyxins, may become antibiotics of last resort.

The major change in the use of aminoglycosides has been a trend toward single daily dosage, even though this is not an FDA-approved dosing regimen. Gentamicin, the most widely administered and the most studied of the aminoglycosides, is the prototype for our discussion.

**Mechanism of Action and Antimicrobial Activity**
The aminoglycosides act in part by impairing bacterial protein synthesis through irreversible binding to the 30S subunit of the bacterial ribosome. They are rapidly bactericidal against a broad range of aerobic gram-negative bacilli (including *P aeruginosa*), but lack activity against anaerobes. Although there is activity against some
gram-positive aerobic cocci, it is unreliable. The aminoglycosides are generally used against gram-positive cocci such as enterococci and staphylococci in combination with beta-lactam antibiotics and vancomycin to achieve synergistic bactericidal activity. This clinical application of drug synergy is based primarily on in vitro and animal studies because there are no comparative trials showing better cure rates with addition of an aminoglycoside.\textsuperscript{107} Synergy is lacking or variable when aminoglycosides are combined with newer drugs such as daptomycin, quinupristin-dalfopristin, or linezolid.\textsuperscript{108}

Acquired resistance to the aminoglycosides is usually mediated by bacterial elaboration of aminoglycoside-inactivating enzymes. These enzymes are widely distributed in both gram-positive and gram-negative bacteria, and usually are plasmid-mediated.\textsuperscript{109} Amikacin is the most likely of all aminoglycosides to be effective against MDR gram-negative bacilli because amikacin only has one locus that is susceptible to aminoglycoside-inactivating enzymes compared with six susceptible loci on gentamicin and tobramycin.\textsuperscript{110,111}

Among gram-positive cocci, the most clinically significant resistance occurs in enterococci, where the synergistic killing activity of aminoglycosides is required for a high cure rate of endocarditis. Although all enterococci are intrinsically resistant to low concentrations of aminoglycosides, the clinical problem arises with high level gentamicin resistant (HLGR) enterococci.\textsuperscript{84} HLGR enterococci are resistant to all other aminoglycosides in clinical use in the United States, with the possible exception of streptomycin, and do not demonstrate synergistic killing of enterococci when aminoglycosides are combined with penicillin or vancomycin.\textsuperscript{84} Detection of HLGR requires either special susceptibility wells or screening plates with high concentrations of gentamicin or streptomycin (eg, $\geq$500 $\mu$g/mL gentamicin; $\geq$1000 $\mu$g/mL streptomycin).

The synergistic killing effect of beta-lactam antibiotics and aminoglycosides has been demonstrated with multiple aerobic gram-negative bacilli and gram-positive cocci and in multiple animal models. In uncontrolled clinical studies, synergistic activity has been demonstrated to be important in the treatment of native valve endocarditis caused by enterococci and in prosthetic valve endocarditis due to \textit{S epidermidis}.\textsuperscript{84} There is a lack of clinical studies to clearly demonstrate benefits of drug synergy with aminoglycosides in serious \textit{P aeruginosa} infections, and in infections caused by gram-negative bacilli in neutropenic patients. The aminoglycosides remain among the most active antibiotics against \textit{P aeruginosa}.\textsuperscript{109}

\textbf{Pharmacokinetics}

Aminoglycosides are poorly absorbed orally. After intravenous infusion of 1.7 mg/kg gentamicin (every 8 hour dosage), peak serum levels (C$_{\text{max}}$) are 4 to10 $\mu$g/mL. After infusion of 5 mg/kg (once daily dosage), peak levels are about 20 $\mu$g/mL serum. The half-life of all of the aminoglycosides is about 2 to 3 hours. Protein binding is low (<10%) and, because the agents are water soluble, they are distributed in the intravascular space and into interstitial fluid. The drugs diffuse into synovial, pleural, and peritoneal fluids, but penetration into CSF and bile is poor.

In general, in the absence of large effusions and edema, the volume of distribution is low. Increases in the volume of distribution tend to decrease the C$_{\text{max}}$ and area under the serum-concentration-time curve (AUC), and increases in clearance tend to decrease the AUC. For example, the volume of distribution tends to be elevated and peak serum levels decreased in patients who have large effusions, fever, burns, or congestive heart failure and in critically ill patients.\textsuperscript{112} Excretion of aminoglycosides is primarily by glomerular filtration; clearance is decreased with renal insufficiency and increased in children, in pregnancy and in patients who have cystic fibrosis.
Pharmacodynamics

The aminoglycosides show the following well-studied pharmacodynamic properties: (1) Concentration-dependent killing, (2) PAE, and (3) Postantibiotic leucocyte enhancement.

Concentration-dependent killing

Bacterial killing by aminoglycosides in vitro is concentration-dependent. In vivo, higher doses of the drug not only increase the rate of reduction of bacteria, but also the length of time of drug exposure to bactericidal concentrations as measured by the AUC. In animal studies, aminoglycoside efficacy is correlated with the ratio of C\text{max} to MIC of the infecting organism and also with the AUC. In animal studies, effective dosing regimens for concentration-dependent antibiotics require that either the 24-hour AUC/MIC be 80 to 100 against gram-negative bacilli or the C\text{max}/MIC of the causative pathogen be 8 to 10.

Some clinical studies have demonstrated a relationship between peak aminoglycoside concentrations and response to therapy. For concentration-dependent drugs, such as aminoglycosides, giving the total daily dose once every 24 hours rather than smaller divided doses would maximize the C\text{max} and possibly allow for comparable or better efficacy at greater convenience and lower cost. A C\text{max}/MIC of 10 to 12 appears to be the optimal ratio to ensure clinical response. To achieve this ratio with single daily dose gentamicin, the MIC must be 2 μg/ml or less and preferably 1 μg/ml or less.

PAE

Aminoglycoside antibiotics have a PAE for both staphylococci and gram-negative bacilli, meaning that suppression of bacterial growth persists despite concentrations of antibiotic below the MIC. This permits longer intervals before another dose of aminoglycoside is given.

Postantibiotic leucocyte enhancement

Enhanced phagocytosis of aminoglycoside-exposed bacteria by host leukocytes has also been observed in vitro. This phenomenon has been referred to as postantibiotic leukocyte enhancement (PALE). The absence of PALE may help explain the decreased efficacy of once-daily dosing that has been described in neutropenic animals as compared with nonneutropenic animals.

The antibacterial effects of aminoglycosides can be impaired in a couple of settings. First, an acidic or an anaerobic environment is known to impair the activity of aminoglycosides. Second, adaptive resistance refers to the phenomenon of transient reduction in rate of bacterial killing by an antibiotic following pre-exposure to that drug. Adaptive resistance to aminoglycoside agents has been observed principally in P aeruginosa, but also in other gram-negative bacilli and more recently in staphylococci. Once-daily dosing may circumvent the possibility of adaptive resistance through the provision of a drug-free interval.

Toxicity

The major adverse effects of the aminoglycosides are nephrotoxicity and ototoxicity. The aminoglycosides mediate toxic damage to the proximal convoluted tubules in the kidneys, and to the cochlear and vestibular bodies of the inner ear. In addition, aminoglycosides can cause neuromuscular blockade due to interference of neurotransmission at neuromuscular junctions. The uptake of aminoglycosides by renal cortical cells appears to be a saturable process. Once proximal tubular cells are saturated with aminoglycoside, the higher peak serum concentrations seen with once-daily dosing should not cause greater intracellular
accumulation of drug than is seen with multiple lower doses. In fact, renal cortical accumulation of gentamicin in rodents is lower following once-daily dosing regimens than after multiple daily doses, and greater increases in serum creatinine are seen with multiple-daily dosing regimens.125

Correlation of increased renal cortical accumulation of aminoglycosides with dosing frequency rather than with peak serum concentrations has been demonstrated in a cohort of human subjects undergoing nephrectomy for cancer.124 There have been many clinical studies of nephrotoxicity of aminoglycosides. A recent review compiled a summary of the results of meta-analyses of once-daily dosing of aminoglycosides versus multiple-daily dosing.113 Although some of these reported a decrease in nephrotoxicity with once-daily dosing, most of the meta-analyses demonstrated no significant decrease in nephrotoxicity.126 However, once-daily administration of aminoglycoside was less likely to result in nephrotoxicity than twice-daily administration in the only randomized double-blind study of aminoglycoside use.127

Increased nephrotoxicity has been observed in the elderly; in patients who have elevated trough levels; with prolonged use; in patients who have diabetes mellitus; with concurrent use of vancomycin, loop diuretics, cyclosporine, and cisplatin; and when the drug is administered at time of rest as opposed to activity.127–130

Aminoglycoside therapy may result in both vestibular and cochlear toxicity.131 In rats (but not in guinea pigs), gentamicin uptake into perilymph, endolymph, and inner ear tissues appears to be a saturable process, as in the kidney.132 It is unknown whether gentamicin uptake is a saturable process in humans and it is unclear whether aminoglycoside accumulation in the inner ear predicts ototoxicity.132

Risk of ototoxicity has been associated with elevated trough levels of aminoglycoside, although some investigators have found no association between drug levels and ototoxicity after controlling for age.133,134 Nonetheless, the suggestion that aminoglycoside uptake into inner ear fluids is saturable has raised the possibility that once-daily dosing of aminoglycosides may decrease ototoxicity. However, most published meta-analyses have reported no difference in ototoxicity between once- and multiple-daily dosing.113

Clinical Indications

The most common indication for aminoglycosides is combination therapy with other antimicrobial agents for serious gram-negative bacillary infections. In addition, the aminoglycosides are important drugs in the treatment of mycobacterial infections and in infections caused by less common pathogens, such as Yersinia pestis, Brucella spp, and Francisella tularensis.

The aminoglycosides are also used in combination with cell-wall–active antibiotics to provide synergistic bactericidal activity in treatment of serious gram-positive coccical infections such as staphylococcal, enterococcal, and streptococcal endocarditis.84

The major change in therapy with aminoglycosides has been the increasing use of single daily dosage for treatment of gram-negative bacillary infections versus divided daily doses. For example, the daily dose of gentamicin is usually 5 mg/kg. It can be given as 5 mg/kg in one single daily IV dose over 30 to 60 minutes or as 1.7 mg/kg IM or IV every 8 hours in gram-negative meningitis (FDA approved). Once-daily dosing should be performed in a manner that ensures a high $C_{\text{max}}/\text{MIC}$ ratio for the pathogen being treated and ensures that trough levels are low enough to minimize toxicity and permit the loss of adaptive resistance. Maximizing concentrations of aminoglycosides by using single daily dosing optimizes the rate and extent of bactericidal activity and results in lower residual bacterial counts and longer intervals before significant regrowth occurs.
The potential for increased efficacy with once-daily aminoglycoside dosing has been evaluated in a multitude of randomized clinical trials. In general, these individual trials have lacked sufficient power to determine whether observed differences in efficacy between once-daily and multiple-daily dosage regimens were due to chance alone. Therefore, meta-analysis has been used to synthesize the data contained in these multiple studies. Most meta-analyses demonstrated an improvement (albeit small) in the clinical efficacy of once-daily aminoglycoside dosing.113

Overall, in vitro, animal, and existing clinical data suggest that once-daily administration of aminoglycosides may be more efficacious and less nephrotoxic, or at least not more nephrotoxic, than multiple-daily dosing. Giving the total 24-hour dose as a single dose, rather than in smaller divided doses, and using extended dosing intervals has now become the standard for use in gram-negative bacillary infections in many clinical settings.113 This strategy may be especially appropriate for treatment of infections caused by borderline susceptible pathogens (eg, *P aeruginosa*), with MICs that are close to the breakpoint.135

The dosages of once-daily administration of gentamicin, netilmicin, and tobramycin have varied from 4–7 mg/kg/day in clinical trials.135 A starting dose of 5 mg/kg has been suggested for adults 30 to 60 years of age with doses of 6 mg/kg for adults below 30 years and 4 mg/kg for those over 60.113 Because of patient-to-patient variability, 4 mg/kg dosing does not always ensure sufficiently high peak concentrations to provide optimal activity against organisms such as *P aeruginosa*.135 The use of 7 mg/kg dosing of gentamicin in 2148 adult inpatients was associated with only 27 incidents of nephrotoxicity and 3 of vestibulotoxicity; however, the median duration of therapy was only 3 days.135 It has been suggested that the initial once-daily doses should be 7 mg/kg for gentamicin and tobramycin and 15 mg/kg for amikacin in the critically ill; the dose is then tapered to yield a Cmax/MIC greater than or equal to 10.109 Other investigators have suggested a dose of 5 mg/kg for gentamicin, which is more in line with the FDA-approved daily dosage.106

Two different approaches have been suggested to treat patients who have impaired renal function: reduction of daily drug dosage, and increase in dosing interval beyond 24 hours.135,136 Intuitively, it seems most reasonable to give daily doses that will yield peak serum levels that result in an appropriate Cmax and to stop administration as soon as feasible. Regardless of the approach used, vigilant monitoring of aminoglycoside serum levels is of utmost importance when renal function is decreased.

The doses of aminoglycosides used for synergistic bactericidal activity in the treatment of gram-positive coccal endocarditis have been lower than those used for serious gram-negative infections (target serum peak level of gentamicin 3 μg/mL). The most compelling data on the need for synergistic bactericidal activity requiring aminoglycosides concern enterococcal endocarditis. Although a significant PAE has been demonstrated against enterococci with aminoglycoside/beta-lactam combinations in vitro, no PAE was demonstrated in an animal model of enterococcal endocarditis.137 Animal models of enterococcal endocarditis using single daily doses of aminoglycosides compared with 8-hour doses have yielded conflicting results.84 The current recommendations from the American Heart Association state that until more data demonstrate that once-daily dosing of an aminoglycoside is as effective as multiple-daily dosing, gentamicin or streptomycin should be administered in multiple divided doses rather than a daily single dose to patients who have enterococcal endocarditis.84

Aminoglycoside antibiotics have been used in the treatment of pulmonary exacerbations in patients who have cystic fibrosis and *P aeruginosa* colonization.138–141
Antibiotic treatment of such exacerbations is typically prolonged, and often occurs in the home setting. Once-daily dosing for home therapy has obvious advantages. Evidence also suggests that inhaled tobramycin can reduce infective exacerbations and other health care costs in cystic fibrosis patients.\textsuperscript{142–144} Debate continues, however, over whether aminoglycoside therapy significantly contributes to the long-term risk of nephrotoxicity in cystic fibrosis patients.\textsuperscript{145}

Patients who have cystic fibrosis clear aminoglycosides at an increased rate.\textsuperscript{146} Higher doses of aminoglycosides (eg, tobramycin at doses up to 15 mg/kg/d) once daily have been used successfully with little or no increase in nephrotoxicity,\textsuperscript{147–152} although transient ototoxicity has been associated with these doses.\textsuperscript{148}

Several different methods of monitoring once-daily aminoglycoside dosing have been suggested. Some investigators have suggested monitoring trough concentrations only, with dose adjustments for troughs greater than 2 $\mu$g/mL.\textsuperscript{153,154} However, this approach does not allow clinicians to appreciate underdosage of drug, and trough levels of 2 $\mu$g/mL are too high and indicate reduced clearance with once-daily dosing.

Another proposed approach to monitoring of once-daily dosage is with a drug level taken 6 to 14 hours after infusion and adjusting the doses according to a nomogram.\textsuperscript{135,155,156} Suboptimal peaks are not recognized by this method. A third approach measures two levels (at 0.5–1 h and 6–14 h) and calculates the AUC.\textsuperscript{157–159}

It has been proposed that aminoglycoside levels need not be measured with once-daily dosing in patients who have ClCr greater than 60 mL/min who receive fewer than 5 days of therapy.\textsuperscript{135,160} However, levels should be checked in patients at increased risk for toxicity or clinical failure, such as the elderly, those receiving other nephrotoxic drugs, those with severe infections, or those expected to require longer than 5 days of treatment. In patients on long-term therapy, aminoglycoside levels should be measured weekly as long as the serum creatinine is stable.\textsuperscript{135,160}

**SUMMARY**

This article reviews three classes of antibacterial agents that are uncommonly used in bacterial infections (other than mycobacterial infections) and therefore can be thought of as special-use agents. The polymyxins are reserved for gram-negative bacilli that are resistant to virtually all other classes of drugs. Rifampin is used therapeutically, mainly as a companion drug in treatment of refractory gram-positive coccal infections, especially involving foreign bodies. Rifaximin is a new rifamycin that is a strict enteric antibiotic approved for use for treatment of traveler’s diarrhea and is showing promise as a possible agent for refractory \textit{C difficile} infections. The aminoglycosides are used mainly as companion drugs for the therapy of resistant gram-negative bacillary infection and for gram-positive coccal endocarditis. The major change in use of aminoglycosides has been a shift to once-daily dosing in many situations.

**REFERENCES**


