patients with a history of penicillin allergy are found to have negative skin test results, the risk for reacting to a cephalosporin is negligible. Studies involving patients with a history of penicillin allergy and positive penicillin skin testing results who subsequently received cephalosporins have found an overall reaction rate of 2%. Cross-reactivity between penicillins and cephalosporins can be predicted based on the presence of similar R1 side chains, such as occurs between ampicillin/amoxicillin and cephalexin/cefadroxil, in the range of 10% to 38% (Table 23.1).[45–48] Although most patients tolerate the corresponding cephalosporin, anaphylactic reactions have been noted. For these and other higher-risk patients, graded cephalosporin challenges can be performed to ensure tolerance.[44,49] Subjects with an IgE-mediated hypersensitivity to penicillin can be treated with cephalosporins with dissimilar side chains.[50] Third-generation cephalosporins can be used in patients with a history of nonimmediate or non–life-threatening allergy to penicillin. Fig. 23.1 outlines a suggested approach to patients with penicillin allergy in need of other β-lactams.

Conversely, in patients evaluated after an immediate allergic reaction to cephalosporins, the rates of positive results of testing for reactions to penicillin determinants have been found to be 4.8% to 25.5% in various series.[51–53] However, the studies with higher rates of sensitization were not confirmed in most patients by subsequent clinical challenges. If penicillin skin testing is not available, graded challenges may be performed starting with $\frac{1}{10}$ of the therapeutic dose. Only 1% to 3% of cephalosporin-allergic patients have positive results of skin tests for carbapenems or aztreonam.[51] Among the different kinds of cephalosporins themselves, the R1 side chain is an important antigenic determinant, and cross-reactivity must be considered in terms of structural similarity.[40,53] Of note, important cross-reactivity has been detected among ceftriaxone, cefotaxime, and cefepime, which share an identical side chain at the R1 position.[53–55] Recent work by Romano and colleagues demonstrated that patients with cephalosporin allergy commonly tolerated a different cephalosporin of varied R1/R2 side chain.[37]

Fig. 23.2 outlines a suggested approach to patients with cephalosporin allergy who are in need of other β-lactams.

The first study to determine the potential for cross-reactivity between carbapenems and penicillins based on skin testing estimated a frequency of approximately 50% in penicillin skin test–positive patients.[56] Subsequent clinical studies of penicillin-allergic patients have evidenced progressively lower rates, 0% to 11% for imipenem and meropenem,[57–59] in patients with histories of penicillin allergies. A systematic review found a 2.4% to 4.3% rate of hypersensitivity response to carbapenems in patients with penicillin IgE-mediated allergies.[60] The lowest rates (0%) have been noted in prospective studies of penicillin skin test–positive subjects (all carbapenem skin test negative) who were challenged with carbapenems in clinical studies. Higher incidences (6%–11%) of reactions have been reported in retrospective studies of patients with reported

TABLE 23.1 β-Lactams With Common Side Chains

Five Groups of β-Lactams With Common R1 Side Chains		
COMMON AMINOBENZYL GROUP	**COMMON AMINOBENZYL GROUP**	**COMMON METHYLENE GROUP**
Amoxicillin Cefadroxil Cefatrizine Cefprozil	Ampicillin Cephalexin Cefaclor Cephradine Cephaloglycin Loracarbef	Benzyl penicillin Cephalothin
COMMON METHOXYIMINO GROUP	**COMMON AMINOTHIAZOLE GROUP**	
Ceftriaxone Cefuroxime Cefotaxime Cefepime	Ceftazidime Aztreonam	
Six Groups of β-Lactams With Common R2 Side Chains		
Cephalexin Cefadroxil Cephradine	Cefotaxime Cephalothin Cephaloglycin	Cefuroxime Cefoxitin
Cefotetan Cefamandole Cefmetazole Cefpiramide	Cefaclor Loracarbef	Ceftibuten Ceftizoxime

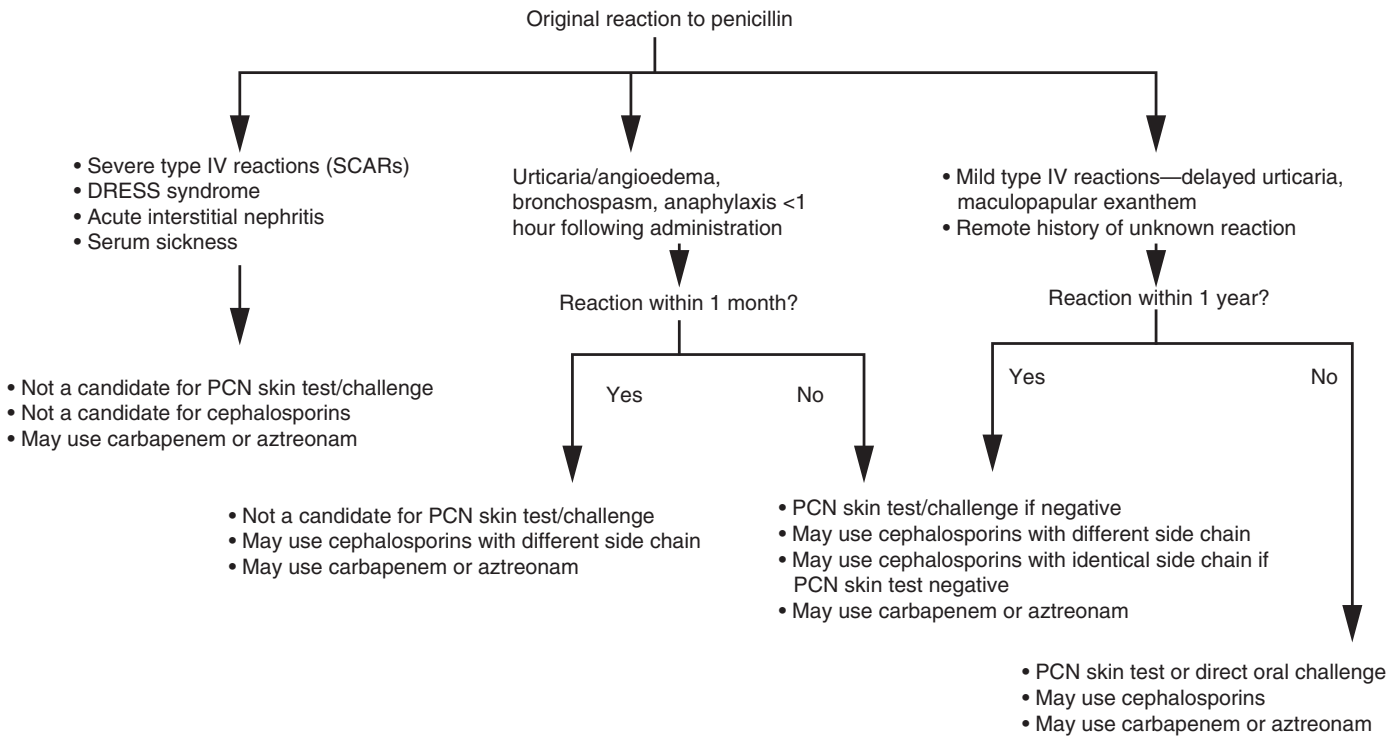

FIG. 23.1 Approach to the use of β-lactams in patients with a history of penicillin allergy. *DRESS,* Drug rash with eosinophilia and systemic symptoms; *PCN,* penicillin; *SCAR,* severe cutaneous adverse reaction.

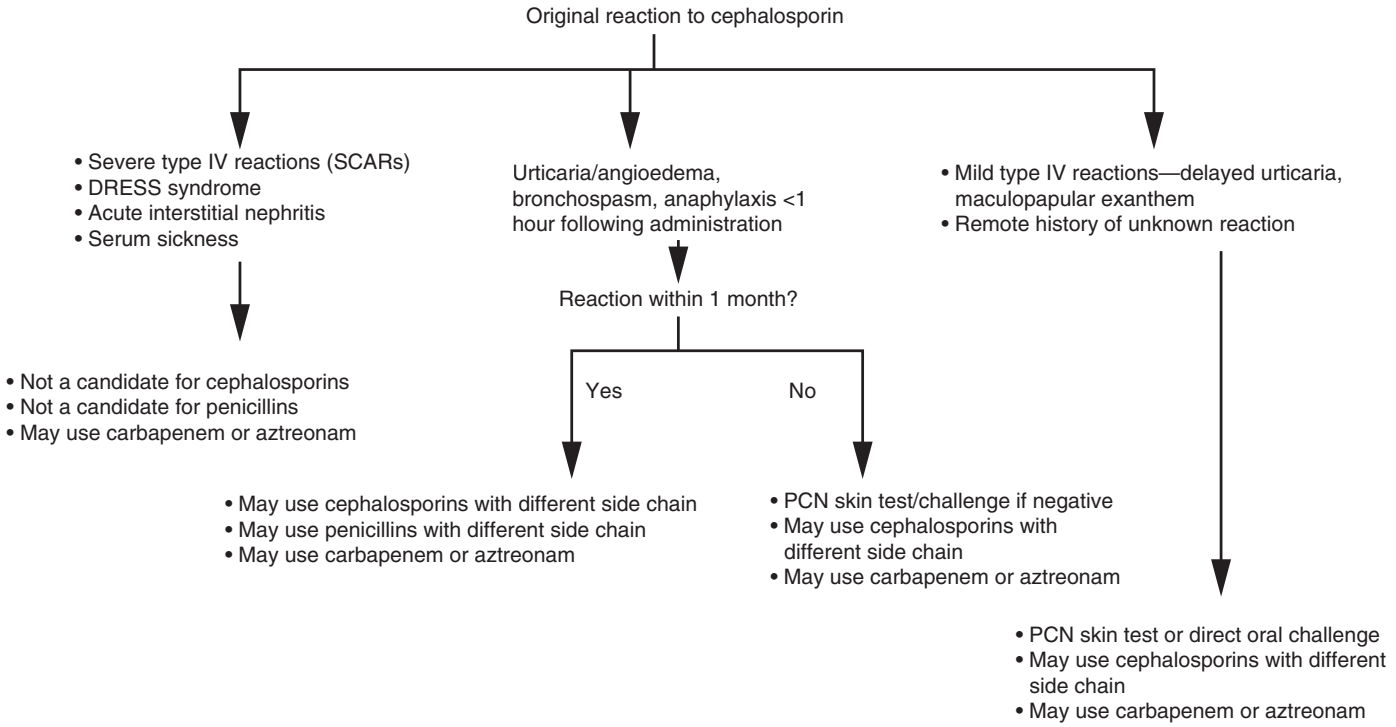

FIG. 23.2 Approach to the use of β-lactams in patients with a history of cephalosporin allergy. *DRESS,* Drug rash with eosinophilia and systemic symptoms; *PCN,* penicillin; *SCAR,* severe cutaneous adverse reaction.

penicillin allergy who received carbapenems. This discrepancy in rates may be due to potential confounding factors in the retrospective reports. Carbapenems may be safely administered in patients with negative results of skin tests for both penicillins and carbapenems. A typical approach for penicillin-allergic patients (when penicillin skin tests are unavailable or the results are positive) is to administer $\frac{1}{10}$ of the carbapenem, and, if tolerated, administer the rest of the therapeutic dose 1 hour later.

The tolerability of aztreonam in populations with IgE-mediated hypersensitivity to β-lactams has been well established,[61] except with a history of reactions to ceftazidime by reason of identical side chains.

In conclusion, in most instances there is minimal evidence for clinical cross-reactivity among various classes of β-lactams. The highest reported rate is in skin test–positive cephalosporin-allergic patients, in whom 25% have positive penicillin skin test results. It should be noted that this cross-sensitization at skin testing does not always translate into true clinical reactivity on subsequent challenge.

Sulfonamides

Pathophysiology

Sulfonamide antibiotics contain an SO_2-NH_2 group that is metabolized to reactive, haptenic nitroso compounds in the liver. IgE-mediated reactions are infrequent, and most cases are due to T-cell–mediated reactions.

Clinical Manifestations

Although maculopapular exanthems are the most common form of drug allergy with sulfonamides, they are an established cause of more serious reactions, such as SJS and TEN or DRESS. In fact, trimethoprim-sulfamethoxazole (TMP-SMX) was implicated in 66.6% of cutaneous drug reactions requiring hospitalization in one study.[62] Of note, TMP-SMX has also been observed to have a much higher reaction rate in the HIV-infected population, mostly in the form of exanthems.[63]

Diagnosis

Skin testing with sulfonamides lacks good predictive value. As with other drugs, graded challenges can be performed if the likelihood is low for true allergy.[64] Most experts believe that testing for sulfonamide allergy should be approached with caution because of the well-known propensity of these drugs to cause SCARs.

Treatment

In nonimmediate reactions with mild rashes, especially in HIV-positive individuals, the antibiotic can be continued ("treating through") or readministered after a gradually increasing dosing protocol, with good success rates (54%–100%).[65] Such reactions are not IgE mediated, but the term *desensitization* has been used to describe the various protocols to induce tolerance to TMP-SMX. Furthermore, these so-called desensitization procedures may or may not truly induce drug tolerance and do require monitoring for more serious systemic involvement. Other studies have shown similar rates of success in achieving a therapeutic dose by simply rechallenging patients versus using a "desensitization" procedure.[66,67] A 6- or 14-step graded administration over 1 day in patients without HIV was successful in 89% to 98% of patients, who were able to start therapy with TMP-SMX.[68] Whether a simple rechallenge in these non–HIV-positive patients would be similarly effective has not been studied.

Vancomycin

One of the most common adverse reactions to vancomycin is the infusion-related red man syndrome, which is secondary to direct mast cell activation and histamine release. It is related to the rate of infusion and typically manifests as pruritus and erythematous flushing, particularly of the face and neck. In some cases, urticaria, angioedema, and even hypotension may also occur but may not always be IgE mediated. These pseudoallergic reactions can be prevented by slowing the rate of infusion and premedicating with H1 blockers. Concomitant opiates can also contribute to these pseudoallergic reactions. Desensitization protocols have been described for both IgE-mediated and non–IgE-mediated hypersensitivity reactions. Linear IgA bullous dermatosis (LABD) is the most commonly identified hypersensitivity reaction to vancomycin; it is an autoimmune, subepidermal vesiculobullous reaction typically associated with the use of vancomycin[69] that resolves with drug withdrawal. Mucosal lesions may be confused with SJS. Case reports of DRESS syndrome and acute interstitial nephritis (AIN) have also been published.[70]

Fluoroquinolones

Because of the increased recent use of quinolones, a history of quinolone allergy is becoming more frequent. Immediate hypersensitivity to quinolones has been estimated to range from 0.4% to 2%, with delayed exanthems being a more common reaction.[71] Quinolones are capable of causing non–IgE-mediated histamine release through MRGPRX2, and this mechanism is thought to participate in pseudoallergic reactions, which cannot be demonstrated through skin testing. Moxifloxacin has been shown to increase the odds of immediate hypersensitivity by fourfold compared with other quinolones.[72] Skin testing has not been validated to provide useful information regarding this nonspecific histamine release, which is induced at even minimal concentrations. BAT has been studied for in vitro diagnosis, and ciprofloxacin shows a higher sensitivity than moxifloxacin, even when moxifloxacin is the culprit drug. Drug challenges remain the cornerstone of diagnosis. The necessity for DPT is evident from the fact that only 7% to 32% of patients with suspected immediate and delayed reactions to quinolone who underwent DPT could be confirmed as allergic.[73,74] There are reports of cross-sensitization among the different quinolones, but the true rate of this apparent cross-reactivity is unclear. Limited data suggest that levofloxacin may be the most reasonable alternative.[75]

Macrolides

A history of allergic reactions to macrolides is rare. These reactions develop in 0.4% to 3% of the treated population. Macrolide hypersensitivity is clearly overestimated but rarely reproduced with oral challenge. On the basis of DPT results in the literature, 90% of these patients are unnecessarily avoiding these antibiotics.[76,77] Although skin or in vitro testing may be an adjunctive strategy to verify tolerance, these methods have little value as diagnostic tools. Drug challenge is the most important diagnostic tool in management and should be considered based on a favorable risk-benefit assessment.[78]

Aminoglycosides

Although topical aminoglycoside antibiotics are common causes of allergic contact dermatitis, systemic hypersensitivity is unusual and descriptions have mostly been limited to isolated reports of anaphylaxis to various compounds such as gentamicin and tobramycin.[79,80]

ANTIBIOTIC ALLERGY AND ANTIMICROBIAL STEWARDSHIP

Unverified penicillin allergy in hospitalized patients has several negative impacts on antibiotic optimization, including increased treatment costs, antibiotic resistance, and a heightened risk of *Clostridioides difficile* (formerly *Clostridium difficile*) infection and other adverse effects. There has been a recent surge in reports dealing with the important topic of antibiotic allergy labeling and delabeling, with implications for future care and outcomes. Penicillin allergy testing is now recommended as part of an effective antibiotic stewardship program. Many hospitals are developing dedicated multidisciplinary antibiotic allergy delabeling teams, involving the expertise of pharmacists, allergists and immunologists, and infectious disease physicians, and using computer-derived algorithms to stratify patients.[81,82] A decrease in the use of alternative antibiotic classes has been noted in parallel with penicillin allergy delabeling. However, treatment algorithms vary across health care systems, and this current divergence is not conducive to a standardized approach. The allergy and infectious disease communities need a consensus guideline for the evaluation of all patients with suspected penicillin allergy.

MULTIPLE DRUG INTOLERANCE SYNDROME

Multiple drug intolerance syndrome has been defined to include patients with reactions to three or more drugs that are not structurally or pharmacologically related. In studies of these patients, confirmation of true allergy is often lacking, and reactions are driven by anxiety (rather than IgE-mediated reactions).[83,84] Many patients may have subjective symptoms of their drug reactions. Evaluation of these patients typically requires blind, placebo-controlled drug challenges.

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24 Fusidic Acid

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SHORT VIEW SUMMARY

- Fusidic acid is an antimicrobial largely used for oxacillin-resistant *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA]), although drug susceptibility is much broader (see Table 24.1). Drug resistance arises rapidly in MRSA when fusidic acid is used alone.
- Nearly complete absorption from the gastrointestinal tract and few side effects or drug interactions (except with statins) have made fusidic acid useful in soft tissue infections, in combination with another active agent such as rifampin (see Table 24.2).
- Metabolism is largely by the liver, and no useful amount of bioactive drug is in the urine.
- Fusidic acid inhibits hepatic pathways of statin metabolism, which may lead to rhabdomyolysis.
- Topical preparations for the skin and conjunctiva have been useful, although they have been linked with widespread emergence of resistance.
- Fusidic acid (CEM-102) is not available in the United States; as of this writing it is undergoing phase III clinical trials.

STRUCTURE AND MECHANISM OF ACTION

Fusidic acid (in the United States, CEM-102) is an antibiotic derived from the fungus *Fusidium coccineum* and the only commercially available antibiotic from the fusidane group. It has a steroid structure, without steroid activity and with chemical similarities to cephalosporin P1. (Fig. 24.1) The sodium salt of fusidic acid (sodium fusidate) is used clinically and was developed in Denmark by Leo Laboratories and introduced into practice in 1962, primarily as an antistaphylococcal therapy.[1–3]

Fusidic acid is a bacteriostatic antibiotic, with bactericidal properties at higher concentrations. Its mode of action is via inhibiting bacterial protein synthesis[4]—primarily by blocking the translocation of peptidyl transfer RNA to the growing peptide chain (elongation phase) via impeding the action of the elongation factor G (EF-G) on the ribosome. Subsequent reductions in surface proteins render organisms such as staphylococci more susceptible to phagocytosis.[5]

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of fusidic acid is summarized in Table 24.1. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides clinical breakpoints (see Table 24.1), with a minimal inhibitory concentration (MIC) breakpoint of less than or equal to 1 µg/mL as susceptible for *Staphylococcus aureus* (99.7% for methicillin-resistant *S. aureus* [MRSA] strains; 99.3%–99.9% for multidrug-resistant *S. aureus* phenotypes).[6] A number of authors have described MICs and zone diameters for fusidic acid against staphylococci, assigning less than or equal to 0.5 µg/mL as susceptible and greater than or equal to 2 µg/mL as resistant (≥21 mm susceptible, ≤17 mm resistant for zone diameters).[7–9] Thus, routine susceptibility testing methods appear to provide comparable accurate results for fusidic acid against *S. aureus.*[10]

Overall, fusidic acid has a narrow spectrum with activity against gram-positive bacteria such as staphylococci, including MRSA and coagulase-negative staphylococci; *Clostridium* spp., including *C. tetani, C. perfringens,* and *C. difficile*; *Corynebacterium* spp.; *Peptostreptococcus* spp.; and most anaerobes except *Fusobacterium* spp. It has some activity against streptococci[11] and limited activity against enterococci. Gram-negative organisms are generally resistant, except for *Neisseria* spp., *Legionella pneumophila,* and some anaerobic gram-negative organisms.[11,12] A study found reasonable in vitro activity against multidrug-resistant strains of *Neisseria gonorrhoeae,* and *Chlamydia trachomatis,* raising the possibility of fusidic acid as a treatment option for associated sexually transmitted diseases, although clinical studies are lacking.[13]

Despite having some in vitro activity against *Mycobacterium tuberculosis*[11] and *Plasmodium falciparum,*[14] this has no clinical relevance. Limited activity against *Mycobacterium leprae*[15,16] and *Coxiella burnetii*[17] has been noted, but therapeutic efficacy requires exploration.

RESISTANCE

The mechanisms of resistance to fusidic acid have been reviewed.[18,19] Although fusidic acid resistance was recognized during drug development,[20] only modest rates of resistance were noted globally until the past 10 years or so.[18,21] Subsequently, resistance emergence has been largely linked to the increased use of fusidic acid monotherapy (especially in topical ointments).[6,18] Such isolates display enhanced "fitness" and are often clonally linked.[22,23] Although there is no known cross-resistance between fusidic acid and other antibiotic classes, the barriers to developing resistance are low because only a single point mutation is required.[24,25]

Information regarding fusidic acid resistance is largely based on research associated with staphylococci. Overall, the mean rate of fusidic acid resistance is approximately 5% in this species. It is higher in regions with increased topical fusidic acid use (Europe > United States/Australia),[26–30] especially among burn patients treated with chronic monotherapy.[21] Rates of fusidic acid resistance among *S. aureus* strains are up to 78% in dermatology patients exposed to prior topical fusidic acid monotherapy,[29] with outpatient topical fusidic acid prescribing associated with high rates of fusidic acid–resistant methicillin-susceptible *S. aureus.*[18,31] Previously, in the United States, where fusidic acid use has been limited largely to clinical trials, the rate of resistance (MIC ≥2 µg/mL) among *S. aureus* strains was 0.3%, but for coagulase-negative staphylococci it was 7.2%.[26] An assessment of over 2000 isolates in the United States demonstrated that fusidic acid inhibited 99.8% of *S. aureus* isolates at ≤1 µg/mL.[32]

Traditional resistance to fusidic acid is mediated via various mutations in the *fusA* gene that encodes EF-G, a guanosine triphosphatase that binds the ribosome and catalyzes the final step of peptide chain elongation.[33–35] Fusidic acid binds EF-G, preventing release from the ribosome and ongoing protein synthesis. At least five other resistance genes have been identified *(fusB-F).* The genes *fusB, fusC, fusD,* and *fusF* are thought to encode proteins that protect EF-G,[22,36–38] whereas *fusE* encodes a secondary fusidic acid binding region, *rplF* (ribosomal protein L6).[39] *fusB* and *fusC* are elements that can be chromosomal or plasmid mediated (plasmid puB101). A combination of *fus* resistance mutations does not appear to translate into increased resistance.[22] Fusidic acid–resistant *S. aureus* generally has detectable resistance mechanisms (*fusA, fusB, fusC,* and *fusE*),[6] particularly if MIC values are greater than or equal to 4 µg/

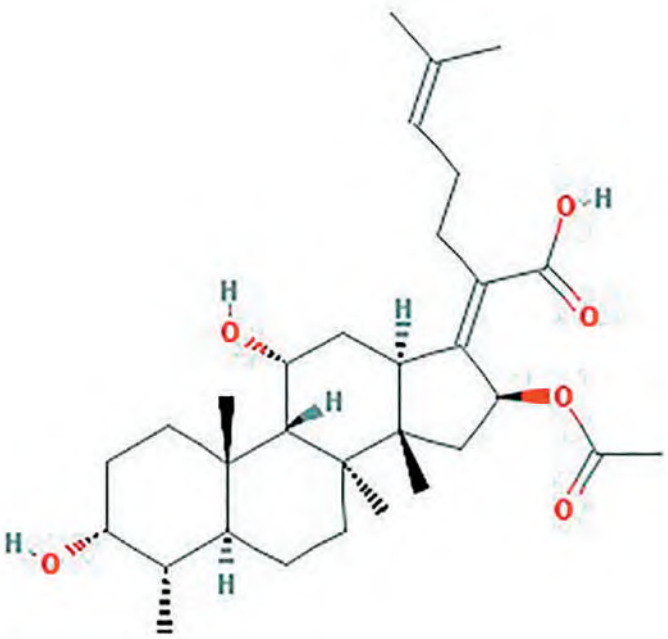

FIG. 24.1 Chemical structure of fusidic acid.

mL. Throughout Europe and Scandinavia, chromosomal *fusB* resistance mutants have been associated with epidemic clonal outbreaks.[22,23,40,41] In New Zealand, the emergence of a fusidic acid–resistant MRSA clone harboring the *fusC* gene was associated with increased topical fusidic acid use nationally.[42–44] Fusidic acid resistance has also been noted to occur in non–multidrug-resistant strains of community-associated MRSA.[45,46] Resistance due to *fusC* has also been reported in other staphylococcal species, including *S. hominis* subsp. *hominis, S. epidermidis, S. haemolyticus,* and *S. capitis* subsp. *ureolyticus.*[44] Meanwhile, *fusA* has also been described in *Clostridium* spp., *Bacillus* spp., and *Salmonella enterica.*[47] In some lesser susceptible β-hemolytic streptococci strains, the resistance mechanism remains unknown, despite apparent clinical treatment response in soft tissue skin infections involving streptococci.[2]

Gram-negative bacilli appear to be inherently resistant to fusidic acid owing to an inability of the drug to penetrate the cell wall, although in cell wall–free *Escherichia coli* systems, fusidic acid inhibits protein synthesis.[48] Other mechanisms of fusidic acid resistance include binding and sequestering of fusidic acid by the type 1 chloramphenicol acetyltransferase found in Enterobacteriaceae, deacetylation by an esterase produced in *Streptomyces* species,[21] and efflux by the AcrAB efflux system in *E. coli*.[49]

ADMINISTRATION AND DOSING

The modes of administration and dosing are shown in Table 24.2. Fusidic acid can be administered as an oral, an intravenous, or a topical formulation and has been used in antibiotic-impregnated gauze, tulle, or wicks.

TABLE 24.1 In vitro Activity of Fusidic Acid Against Common Pathogens Using EUCAST Criteria

ACTIVITY	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC (RANGE) (μg/mL)	MIC BREAKPOINT (μg/mL)[a]	REGIONS OF EMERGING RESISTANCE AND COMMENTS
Gram Positive					
MSSA	0.06[11] 0.06[87] 0.12[6]	0.06[11] 0.125[87] 0.25[6]	0.06–0.12[11] <0.015–0.124[87] —	1 1 1	Limited *Staphylococcus aureus* resistance in United States (0.35%), Australia, and Canada (7%)[6,26] Highest rates in Greece (52.5%), Ireland (19.9%), United Kingdom (11.8%). 1%–3% *S. aureus* resistance in Germany, Israel, Italy, Poland, Spain, and Sweden[26]
MRSA	0.06[11] 0.125[93]	0.06[11] 4[93]	0.03–8[11] 0.03–8[93]	1 1	New Zealand[42]
hVISA	—	—	0.03–8[93]	1	
CoNS	0.12[11]	0.25[11]	0.03–8[11]	1	Overall CoNS resistance (2.5%) > *S. aureus*[7] CoNS resistance highest in Ireland (50%), France (49.4%), Switzerland (47.4%), and Belgium (42.9%) isolates[26]
Staphylococcus epidermidis	0. 2[11] 0.25[7]	0.25[11] 0.5[7]	0.03–8[11] <0.12–4[7]	1 1	
Staphylococcus saprophyticus	4[7] 4[8]	4[7] 4[8]	0.12–4[7] 2–8[8]	ND ND	*S. saprophyticus* intrinsically resistant (*fusD* mutation)[22]
Enterococcus spp.[b]	25[6]	25[6]	12->8[6]	IE	
Enterococcus faecalis	4[7] 25[94]	8[7] 25[94]	1–32[7] 3.12–25[94]	ND ND	*E. faecalis* resistant to fusidic acid, 99.3% in one study[93]
VRE	4[95]	4[95]	2–16[95]	ND	
Corynebacterium jeikeium	0.03[96]	0.06[96]	ND	ND	No data available for *Corynebacterium diphtheriae*
Micrococcus luteus	—	—	0.25-0.5	ND	
Streptococcus pneumoniae	8[94] 2[96]	8[94] 4[96]	2-8[94] ND	ND ECOFF < 32[96]	
Streptococcus agalactiae	16[6] 8[94]	16[6] 8[94]	16[6] 4-8[94]	32[6] ND	Despite increased MIC values, β-hemolytic streptococci have been clinically responsive to fusidic acid therapy[2]
Streptococcus pyogenes	2[96] 4[6]	4[96] 8[6]	ND 1-8[6]	IE ECOFF < 16[96]	
Gram Negative[c]					
Bacteroides fragilis	2[97]	2[97]	ND	ND	
Enterobacteriaceae	>100[11]	—	—	IE	Aerobic gram-negative bacilli inherently resistant
Haemophilus spp.	—	—	8–32	ND	

Continued

TABLE 24.1 In vitro Activity of Fusidic Acid Against Common Pathogens Using EUCAST Criteria—cont'd

ACTIVITY	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC (RANGE) (μg/mL)	MIC BREAKPOINT (μg/mL)[a]	REGIONS OF EMERGING RESISTANCE AND COMMENTS
Legionella spp.	—	—	—	IE	No available data despite case report evidence of treatment success
Moraxella catarrhalis	0.12[94]	0.12[94]	0.06–0.12[94]	ND	
Neisseria gonorrhoeae	0.6[98]	2[98]	0.25–2[98]	ND	
Neisseria meningitidis	0.03[99] ≤0.015[86]	0.12[99] ≤0.015[86]	0.015–0.5[99] ≤0.015–0.06[86,99]	ND ND	No reports of global resistance
Prevotella melaninogenica	0.5[97] —	0.5[97] —	<0.25-0.5[97] 0.6-0.12[86,94]	ND	
Anaerobic Gram Positive					
Clostridioides difficile (formerly *Clostridium difficile*)	2[100]	2[100]	0.5–64[100]	ND ECOFF: <2[100]	Fusidic acid not used widely for *C. difficile* owing to rapid inducible resistance due to *fusA* resistance mechanisms
Clostridium perfringens	0.12[101]	0.5[101]	≤0.06–1[101]	ND	
Fusobacterium necrophorum	16[101]	32[101]	16–32[101]	ND	
Peptostreptococcus spp.	0.25[101]	0.5[101]	<0.06–2[101]	ND	
Cutibacterium acnes (formerly *Propionibacterium acnes*)	0.25[101]	1[101]	<0.06–2[101]	ND	
Other					
Actinomyces israelii	6.3[102]	12.5[102]	6.3–25[102]	ND	
Coxiella burnetii	0.5[101]	1[101]	<0.06–2[101]	ND	
Mycobacterium leprae	—	—	—	IE	
Mycobacterium tuberculosis	8[103]	16[103]	4–32[103]	IE	
Nocardia asteroides	3.12	6.25	0.78–6.25	ND	

[a]When available, EUCAST breakpoints were reported; the disk content used for EUCAST was 10 μg.
[b]*Enterococcus* spp. included *E. faecium, E. faecalis,* and 82 other enterococcal species.
[c]Gram-negative bacteria predominately found to have fusidic acid MIC values greater than 32 μg/mL.
CoNS, Coagulase-negative *Staphylococcus; ECOFF,* common epidemiologic cutoff values; *EUCAST,* European Committee on Antimicrobial Susceptibility Testing; *hVISA,* heterogeneous vancomycin intermediate *S. aureus*; *IE,* insufficient evidence that species is a good fusidic acid target; *MIC,* minimum inhibitory concentration; *MRSA,* methicillin-resistant *S. aureus; MSSA,* methicillin-sensitive *S. aureus; ND,* no data; *VRE,* vancomycin-resistant *Enterococcus.*

TABLE 24.2 Dosage and Mode of Administration for Fusidic Acid Therapy

ROUTE	FORMULATION	DOSAGE	FREQUENCY
Oral[a]	Film-coated tablets (fusidate sodium)	500 mg[b]	BID-TID[c]
Intravenous[d]	Fusidate sodium	500 mg (per vial)	BID-TID[c,e]
Topical[f] Cream Ointment Gel	 2% fusidic acid 2% fusidate sodium[g] 2% fusidate sodium	 Small quantity topically	 BID
Ophthalmology	1% viscous eye drops fusidic acid	Topical to conjunctival sac	BID

[a]Available in film-coated tablets or pediatric oral suspension (fusidic acid hemihydrate), recommended with food.
[b]Front-loaded dosing regimens can be used; see "Pharmacokinetics and Pharmacodynamics" section.
[c]BID dosing generally for skin and soft tissue infections. For serious infections, TID dosing recommended.
[d]Dilute with normal saline for administration. Intravenous rarely used clinically owing to excellent oral bioavailability.
[e]Infuse over 2 hours or longer.
[f]In some countries combined with steroid formulation (with hydrocortisone acetate or betamethasone 17-valerate).
[g]Ointment-impregnated sterile gauze squares available.
Modified from references 2,21,51–53,57,104.

Where appropriate, oral administration with film-coated tablets (sodium fusidate) is preferred over intravenous formulations owing to its excellent bioavailability. Bioavailability and tolerability have improved significantly since the advent of film-coated tablets, compared with previously marketed capsules and enteric-coated tablets.[50] Dosing regimens that include a loading dose have gained interest because of possible reductions in emergence of resistant subpopulations and faster attainment of steady state.[51,52]

The routine dose for adults with normal renal and hepatic function (oral, 500 mg three times daily; intravenous, 20 mg/kg/day in two to three divided doses[1,50,53]) does not need to be altered in renal impairment, with routine dosing for hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), and continuous renal replacement therapy (CRRT). However, fusidic acid should be avoided in acute liver disease or severe preexisting liver disease. In chronic liver disease, low albumin levels and reduced protein binding are offset by reduced glucuronidation and excretion. In acute liver disease, in which albumin levels are often normal, higher bilirubin concentrations compete with fusidic acid for the limited glucuronidation mechanism, without being offset by the increased elimination of free fusidic acid usually associated with hypoalbuminemia.[54]

Routine doses can be used in the elderly, unless gastrointestinal intolerance (e.g., nausea) is encountered, in which case a dose reduction from 500 mg three times daily to 500 mg twice daily may be considered. Pediatric patients should receive three divided doses as follows: age 1 year or younger, 50 mg/kg/day; 1 to 5 years, 250 mg three times daily; and 6 to 12 years, 500 mg three times daily.[1]

PHARMACOKINETICS AND PHARMACODYNAMICS

Fusidic acid is highly (95%–97%) protein bound,[1] and oral bioavailability is excellent (91%) with newer film-coated tablets introduced since the 1980s. Older capsule formulations were associated with 69% bioavailability.[1,50,53,55] Thus, it should be noted that older pharmacokinetic studies, which used the capsule formulations and reported intersubject variation, may not be totally representative of the pharmacokinetics of the newer film-coated tablet formulation.[50]

Peak serum levels occur at 2 hours (range, 24–52 µg/mL after a 500-mg dose)[1,53] via both oral and intravenous administration.[56] Food consumption reduces the rate of oral drug absorption and serum levels but not overall absorption.[53,57] The drug is metabolized via the liver, with no bioactive drug in urine.[56,58] A small amount is metabolized and excreted in bile. Fecal excretion is minimal,[58] although there is good intraluminal gut activity against *C. difficile* (see "Clinical Uses" later). The serum half-life ranges from 10 to 16 hours independent of administration mode.[59] Mean serum levels after a 96-hour, 500-mg three-times-daily regimen are 71 µg/mL, with a maximum of 123 µg/mL recorded.[56] Steady state for a 500-mg, twice-daily regimen is achieved in 3 weeks[52] compared with 1 day with regimens that include a loading dose (e.g., up to 1650 mg twice daily on day 1 and 500 mg twice daily thereafter).[52,59,60] In one study that used a 1650-mg loading dose followed by high-dose maintenance therapy (825 mg twice daily), the day 1 and day 8 trough levels were 146 µg/mL and 204 µg/mL, respectively.[59]

Fusidic acid is detectable in phagosomes, has good intracellular activity (40%–100% of extracellular), and performs better at reduced pH.[61] It achieves good tissue, bone, and abscess levels but has limited penetration into normal meninges (Table 24.3) and can accumulate with repeated infusions.[53]

Coadministration of fusidic acid with rifampin may affect the pharmacokinetics of rifampin, potentially increasing available rifampin levels, although data are currently limited.[62] Notably, in a US clinical study of rifampin plus fusidic acid for the treatment of prosthetic joint infections, fusidic acid levels were substantially lower than expected, so the trial was terminated early.[63] However, these findings are inconsistent with decades of successful combination therapy for these and similar prosthetic infections in Europe and Australia; hence, further studies are required in order to investigate this recent observation.[1]

ADVERSE REACTIONS

Key potential adverse reactions are shown in Table 24.4. Overall, fusidic acid use has limited safety concerns, even among patients requiring treatment for extended durations.[64–66] Mild gastrointestinal symptoms have been reported with oral use, and reduced toxicity has been noted with newer formulations. Case reports of hematologic toxicities, including sideroblastic anemia and neutropenia, exist.[67–69] No clear renal toxicities exist, and anaphylaxis is rare.[70] Recent phase II studies purposed for US licensing suggest a similar safety profile for fusidic acid as for linezolid for short-term therapy,[60] with limited adverse events occurring in patients treated for longer than 11 days.[65]

Fusidic acid should be avoided in newborns because its strong protein binding may displace bilirubin and be associated with bilirubin encephalopathy.

Although fusidic acid is generally associated with few drug interactions, rhabdomyolysis secondary to concurrent fusidic acid and statin

TABLE 24.3 Penetration of Fusidic Acid Therapy Into Various Tissues

REGION	PENETRATION	COMMENTS
Adipose tissue	Good	Levels above MIC achieved following oral FA 500 mg TID[105]
Blood	Good	Highly protein bound (95%–97%) with peak serum levels up to 64 times *Staphylococcus* MIC[1]
CSF and CNS	Poor	Limited data to support use owing to poor levels in un-inflamed meninges Animal modeling suggests infiltration in inflamed meninges; however, antagonism may occur with β-lactam therapy[106,107]
Bile and biliary system	Good	Good FA levels noted within bile fluid[50]
Bone and joint	Good	Good penetration into synovial tissue (28%–78% of serum)[108–110] and bone (16%–78% of serum).[50] Likely to be improved since the introduction of film-coated formulation in 1980s with increased bioavailability
Soft tissue and muscle	Good	Topical FA penetrates normal, damaged, and avascular skin[111] Oral therapy achieves high levels in blister fluid at BID dosing, burn crusts, and interstitial dermal edema[53,112,113]
Heart tissue and mediastinum	Good	Levels 12- to 20-fold higher than staphylococcal MIC have been isolated from cardiac tissue after FA administration[114,115]
Ocular tissue	Good	Topical FA resulted in corneal tissue levels well above MIC at BID dosing,[116,117] yet poor aqueous humor levels with oral dosing[50]
Placenta	Good	Known to cross the placenta TGA pregnancy category C; use with caution, insufficient data[118]
Prostate	Unknown	No clear in vitro or in vivo evidence for use in prostatitis
Pus	Good	Good levels, slightly lower than that achieved in serum (83% of serum)[50]
Respiratory secretions	Poor	Low FA levels in sputum from cystic fibrosis patients (6%–8% serum)[119]

CNS, Central nervous system; *CSF,* cerebral spinal fluid; *FA,* fusidic acid; *MIC,* minimal inhibitory concentration; *TGA,* therapeutic drug administration.

TABLE 24.4 Adverse Reactions Associated With Fusidic Acid

ADVERSE EVENT	FREQUENCY	COMMENTS
Allergic reactions	U	Allergic responses, including urticaria and atopic dermatitis, are infrequently reported (4.6% of recorded events).[120] No cross-reactivity occurs with β-lactam allergies. Anaphylaxis is rare.
Gastrointestinal and hepatic	C	Gastrointestinal side effects constitute the majority of recorded adverse events associated with fusidic acid (30%–58%). Nausea, vomiting, and diarrhea can occur with oral administration; reduction to twice daily can ameliorate these effects. Up to 30% of patients may have raised bilirubin, usually transient and more frequent with higher doses.[59] The noted rise in bilirubin occurs without fulminant hepatotoxicity and is due to inhibition of bile transport as in Dubin-Johnson syndrome.[a,121,122]
Hematologic	U	Infrequent; immune thrombocytopenic purpura occurs rarely and cytopenias are noted in 7.4% of events.
Neurologic	U	Infrequent; 3.3% of reported events.
Phlebitis	U	Infrequent; generally associated with older IV preparations.
Rash	U	Infrequent; maculopapular rash most common.
Rhabdomyolysis	U	Uncommon, but potentially serious—due to drug interaction with concurrent statin use.[b]

[a]More severe if intravenous dose given too rapidly or if dosing is excessive.[24]
[b]Rosuvastatin, atorvastatin, and simvastatin known interactions (see text for references).
C, Common; *U,* uncommon.

therapy has now been widely reported[71–77] In a recent review, rhabdomyolysis was generally recognized 20 to 30 days after commencement of drug coadministration, usually occurred in patients in their late 60s, and was associated with a 24% to 28% fatality rate.[78] Three pathways (breast cancer resistance protein [BCRP], organic anion transporting polypeptide 1B1 [OATP1B1], and cytochrome P-450 3A isozyme [CYP3A]) are inhibited in liver microsomes, resulting in elevated statin levels.[79,80] Thus, careful monitoring of such patients is required, and in some cases temporary cessation of statin administration should be considered during fusidic acid therapy.

CLINICAL USES

Fusidic acid has predominately been used in countries outside the United States in combination therapy regimens for treatment of staphylococcal infections.[81] Monotherapy is associated with resistance rates of 5.1% compared with 0.8% seen in combination therapy.[18,21,82] Widespread monotherapy use corresponds with high rates of fusidic acid–resistant *S. aureus* isolates and treatment failures.[27,30,83–85]

Various antibiotics have been used in combination with fusidic acid therapy, including rifampin, novobiocin, and β-lactams, although rifampin plus fusidic acid regimens are most common.[18,64,66] Despite discrepancies in historical synergy studies, modern in vitro studies demonstrate improved fusidic acid activity when combined with rifampin and, to a lesser extent, with other antimicrobial combinations (levofloxacin, oxacillin, ceftriaxone, vancomycin, ciprofloxacin, gentamicin).[86] Nonetheless, combination therapy is recommended not primarily for synergy but rather to prevent emergence of resistance.[87] Fusidic acid resistance is low in countries in which combination therapy is used, despite decades of availability.[26,88] The emergence of broadly resistant gram-negative organisms, such as carbapenem-resistant *Acinetobacter baumannii,* have led to reports of in vitro activity when fusidic acid is combined with colistin.[89–91]

The current clinical indications for fusidic acid use are shown in Table 24.5. Primary indications include staphylococcal infections involving skin and soft tissue, bone, and joints. After a period of effective control with intravenous antibiotic therapy, oral fusidic acid in combination with another orally active agent (e.g., rifampin) may provide a suitable treatment option for such infections. Other orally available alternatives with possible activity against *S. aureus* may include linezolid, tetracyclines, and trimethoprim-sulfamethoxazole, but the safety profile of fusidic acid has advantages in many clinical situations, especially when prolonged therapy may be required.[6] Topical fusidic acid therapy has been used for noninfective skin conditions, including eczema; a randomized double-blind placebo-controlled trial demonstrated limited effectiveness,[92] and therefore its use should be discouraged.

TABLE 24.5 Clinical Indications and Recommended Dosage for Fusidic Acid Therapy

INFECTION SITE OR PATHOGEN	DOSING	COMMENTS[a]
Common Indications		
Skin and soft tissue	Systemic therapy 500 mg BID-TID oral	Antistaphylococcal therapy with concurrent streptococci activity; 81%–96% cure rate.[123] FA 500 mg BID achieves blister levels of 79 μg/mL; above staphylococci and streptococci MICs.[2] Similar cure rates with FA compared with flucloxacillin therapy.[1,65] Similar efficacy, tolerance, and end-of-treatment resistance when loading dose FA regimens compared with linezolid therapy for soft tissue infections.[60] A randomized controlled trial of FA with rifampin versus standard of care was terminated early owing to concerns of low FA levels[63] in the combination therapy arm (n = 6); the impacts of reduced dosage and implications for clinical efficacy are uncertain (these findings appear inconsistent with other reports—see text for details).
	Topical	Effective therapy for superficial staphylococcal soft tissue infections,[18] with equal or greater efficacy to oral FA for limited impetigo.[124] Review of overall effectiveness reported to be 82%–100%.[123] FA successful for impetigo treatment, with 2% therapy as effective as mupirocin[125] or retapamulin.[126] Major concerns regarding emerging resistance with topical use; increased FA use associated with the emergence of *Staphylococcus aureus*–resistant clones and impetigo outbreaks across Europe.[18,29,31] Limited end-of-treatment FA resistance after <14 days of topical therapy noted in some populations.[27,123]
Bone and joint	500 mg TID oral[b]	FA not recommended for monotherapy owing to high failure rates.[127] Successful combination therapy for osteomyelitis, septic arthritis, and prosthetic joint infections, primarily involving *S. aureus.*[18] FA commonly used with β-lactam[128] or rifampin.[64,66,81] Successful FA-rifampin therapy for *S. aureus* prosthetic joint infections with prosthetic retention and débridement.[64] Seventy-seven percent 24-month infection-free survival for FA-rifampin therapy in prosthetic joint infections with prosthetic retention; better outcomes in non-MRSA and with longer therapy.[66]
Other Reported Uses		
Endocarditis and bacteremia	500 mg TID IV or oral	For staphylococcal bacteremia, FA is not effective as staphylococci monotherapy and is recommended for use only in combination therapy,[129] generally with rifampin.[18,81] FA–β-lactam or glycopeptide therapy of staphylococci endocarditis is used in some countries, despite limited published evidence.[130] Evidence of in vitro antagonism with penicillin G is of uncertain clinical significance.[c]
Clostridioides difficile (formerly *Clostridium difficile*)	250–500 mg TID oral	FA not superior to standard therapies (metronidazole and vancomycin) in randomized trials. Concerns over higher relapse rates[131,132] and rapid emergence of resistance during therapy.[133,134]
Cystic fibrosis–associated respiratory infections	500 mg BID-TID oral	FA–β-lactam used in *S. aureus* infections in cystic fibrosis patients.[135,136] Prolonged treatment reduced rates of MRSA infections.[137] FA-rifampin–based decolonization regimens have been used in MRSA-colonized patients.[138]
Leprosy	500–750 mg daily	Weak bactericidal antileprosy agent with clinical improvement noted only in case studies.[16] Possible future role in combination *Mycobacterium leprae* therapy. Topical nasal FA reduced smear positivity; usefulness in reducing infectiousness unknown.[139]
Meningitis	Generally not recommended	No conclusive supportive data for FA or FA-β-lactam therapy from in vivo/in vitro animal studies or single retrospective review of efficacy (11 of 104 cases treated with FA).[107,140] If FA required, consider monitoring CSF levels.
Conjunctivitis	1% BID topical drops	Similar efficacy compared with first-line antibiotics in randomized controlled trials.[117,141,142] Similar effectiveness as placebo raises concerns over therapy for conjunctivitis in general.[143]

TABLE 24.5 Clinical Indications and Recommended Dosage for Fusidic Acid Therapy—cont'd

INFECTION SITE OR PATHOGEN	DOSING	COMMENTS[a]
Neisseria spp.	Uncertain	Rising fluoroquinolone resistance may result in FA use in future postexposure *Neisseria meningitidis* prophylaxis.[99] In vitro susceptibility reported for resistant *Neisseria gonorrhoeae;* also in vitro activity against *Chlamydia trachomatis.*[13,86]
Legionella spp.	Uncertain	Addition of FA achieved cure in single case of Legionella pulmonary abscess in renal transplant patient.[144]
Anaerobic infections due to *Bacteroides fragilis*	Uncertain	Effective high-dose therapy (1 g TID) in case series of five patients.[12]
Staphylococcal decolonization	Uncertain	Topical or oral FA therapy does not eradicate *S. aureus.*[82] FA-rifampin therapy was effective at MSSA/MRSA eradication.[137,138]
Surgical prophylaxis	Topical and oral therapy	Not recommended. Lower infection rate vs. placebo in neurosurgical patients given single-dose FA monotherapy[106] and in catheter line prophylaxis[145] without evaluation of impact on resistance. No difference in peritonitis rates in patients with continuous ambulatory peritoneal dialysis[141] or postoperative orthopedic infections when used as prophylaxis.[146] Effective preoperative prophylaxis before ocular surgery with fusidic acid drops (1%).[147,148]

[a]Oral single-agent therapy is not recommended for any clinical indication due to observed rapid emergence of resistance.
[b]In most cases, IV antibiotic (β-lactam or glycopeptide) therapy was used initially and then changed to ongoing oral fusidic acid.
[c]Evidence of failure of flucloxacillin and fusidic acid therapy for staphylococcal endocarditis.[1,130]
FA, Fusidic acid; *MIC,* minimal inhibitory concentration; *MRSA,* methicillin-resistant *S. aureus*; *MSSA,* methicillin-susceptible *S. aureus.*

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The complete reference list is available online at Expert Consult.

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25 Aminoglycosides

James E. Leggett

SHORT VIEW SUMMARY

- Usual intravenous adult dose: 7 mg/kg every 24 hours for gentamicin, netilmicin, and tobramycin; 15 mg/kg for plazomicin; and 20 mg/kg every 24 hours for amikacin
- Usual dose for synergy against gram-positive infections: 3 mg/kg/day gentamicin every 8, 12, or 24 hours
- Renal failure: 60% dose reduction
- Therapeutic drug monitoring: not always necessary for brief administration (<5 to 6 days); trough concentrations should be unmeasurable; typically, two serum concentrations in postdistribution phase (≥1 hour after administration, separated by ≥1.5 half-lives)
- Cerebrospinal fluid penetration: low
- Common adverse effects: nephrotoxicity, ototoxicity
- Contraindications: hypersensitivity
- Drug-drug interactions: increased nephrotoxicity risk with concomitant amphotericin B, clindamycin, foscarnet, furosemide, intravenous radiocontrast agents, and vancomycin
- Indications: atypical mycobacterial infections, brucellosis, cholangitis, cystic fibrosis, diverticulitis, endocarditis, endophthalmitis, meningitis, pelvic inflammatory disease, plague, health care–associated pneumonia, synergy for gram-positive infections, tularemia, urinary tract infections

Aminoglycoside antibiotics have been used since the 1940s, when systematic screening of soil actinomycetes for the elaboration of antimicrobial substances yielded streptomycin. Produced by a species of *Streptomyces,* it was the first antibiotic in the aminoglycoside family (Table 25.1)[1] to be derived, directly or indirectly, from *Streptomyces* spp. (aminoglycosides with names ending in *-mycin*) or from *Micromonospora* spp. (aminoglycosides with names ending in *-micin*). Neomycin, kanamycin, and gentamicin are fermentation products with two or three chemical constituents. Amikacin, netilmicin, and others are semisynthetic derivatives of the natural product. All aminoglycosides share similar physical, chemical, and pharmacologic properties.

Aminoglycosides demonstrate concentration-dependent killing and prolonged postantibiotic effects against susceptible organisms.[2,3] Several members of the aminoglycoside family have predictable in vitro activity against *Pseudomonas aeruginosa* and most other aerobic gram-negative bacilli. Some aminoglycosides have useful activity against mycobacteria; one, paromomycin, has been used to treat selected colonic protozoan pathogens, and a related antibiotic, spectinomycin, has been used to treat infections with *Neisseria gonorrhoeae*. The aminoglycoside antimicrobial activity may be additive to or synergistic with that of β-lactams against infection by aerobic gram-negative bacilli or aerobic gram-positive cocci. Although most studies have failed to demonstrate improved outcomes in patients treated with antibiotic combinations compared with monotherapy,[4,5] patients with septic shock receiving combinations including aminoglycosides showed reduced mortality in a trial and observational study.[6,7] The prevalence of aminoglycoside resistance has remained low,[8] and emergence of bacterial resistance during therapy has been rare. Mean aminoglycoside use in US academic centers declined by 41% from 2002 to 2009, with concomitant significant and opposite change in rates of resistance for some organisms and no change for others.[8]

The members of the aminoglycoside family share the potential for nephrotoxicity, ototoxicity, and, rarely, neuromuscular blockade. Clinically relevant toxicity may be decreasing as shorter drug courses are used. Allergic reactions are rare. Because of patent expirations, the cost of many aminoglycosides is low. The efficacy of the aminoglycosides and resistance problems with newer drugs presage a continued need. More recent reviews have reported that aminoglycoside use is again increasing because of emerging gram-negative resistance to other available drugs.[9–13]

CHEMISTRY

All aminoglycosides have an essential six-membered ring with amino group substituents, hence the name *aminocyclitol*.[1] The descriptor *aminoglycoside* results from the glycosidic bonds between the aminocyclitol and two or more amino-containing or non–amino-containing sugars. Spectinomycin differs in that it has an aminocyclitol ring but no amino sugars and no glycosidic bonds. The central aminocyclitol for streptomycin is streptidine, whereas for all other current aminoglycosides, it is 2-deoxystreptamine. The standard numbering convention is illustrated in Fig. 25.1. The aminocyclitol ring is numbered counterclockwise, and the linked sugar molecules are numbered clockwise. Fig. 25.1 also illustrates the structural basis of the aminoglycoside subgroups. Neomycin and paromomycin are derived from *Streptomyces* spp. and link to cyclic sugars at positions 4 and 5 of 2-deoxystreptamine. Among the commonly used aminoglycosides, neomycin contains the largest number of free amino groups (six). The neomycin family comprises framycetin, neomycin, and paromomycin. All are too toxic for parenteral use. Framycetin is available outside of the United States.

Kanamycin, tobramycin, amikacin, arbekacin, and dibekacin comprise the kanamycin family (Table 25.2). All derive from *Streptomyces* spp. and link to cyclic sugars at positions 4 and 6 of 2-deoxystreptamine. Tobramycin is 3′-deoxykanamycin B. Amikacin is kanamycin A with the semisynthetic addition of 2-hydroxy-4-aminobutyric acid to the amino group at position 1 of the aminocyclitol. Arbekacin and dibekacin are available for clinical use outside of the United States.

Gentamicin is a mixture of C_1, C_{1a}, and the enantiomers C_2 and C_{2a} elaborated by *Micromonospora* spp. with glycosidic linkages at positions 4 and 6. Sisomicin is the dihydro analogue of gentamicin C_{1a}, and netilmicin is derived from sisomicin by the addition of an ethyl group to the amino group at position 1 of the aminocyclitol. Plazomicin is a semisynthetic derivative of sisomicin with the addition of a hydroxy-amino-butyric acid group at the N1 position and a hydroxyethyl substituent at the 6′ amine position. Isepamicin is not approved for use in the United States.

Aminoglycosides are highly soluble in water and insoluble in organic solvents.[14] The latter property correlates with the limited ability of aminoglycosides to cross lipid-containing cellular membranes. Aminoglycosides have a molecular size in the range of 445 to 600 Da.[14] The molecular structure is unchanged by freezing, by heating to 100°C for up to 4 hours, or by alterations in solution pH ranging from 3.0 to 12 over several hours.[15–17] The pK_a values of the individual amino groups can be determined by nuclear magnetic resonance spectroscopy.[18] The overall pK_a for gentamicin is about pH 8.4.[14] Hence, at pH 7.4, the aminoglycosides have a very high positive charge and are cationic.

The overall positive charge contributes to both antimicrobial activity and toxicity. Antibacterial activity is enhanced in media with an alkaline

TABLE 25.1 Family of Aminoglycosides in Clinical Use

GENERIC NAME	PROPRIETARY NAME	SOURCE	YEAR REPORTED	CHEMISTRY
Streptomycin	None	*Streptomyces griseus*	1944	Unique central aminocyclitol ring
Neomycin	Mycifradin, Neobiotic	*Streptomyces fradiae*	1949	Roughly equal proportions of neomycin B and C
Kanamycin	Kantrex	*Streptomyces kanamyceticus*	1957	Mixture of 95% kanamycin A and 5% kanamycin B
Paromomycin	Humatin	*Streptomyces fradiae*	1959	Part of neomycin family
Spectinomycin	Trobicin	*Streptomyces spectabilis*	1961	Chemically distinct but closely related to aminoglycosides
Gentamicin	Garamycin	*Micromonospora purpurea and Micromonospora echinospora*	1963	Roughly equal proportions of gentamicin C_1, C_{1a}, and enantiomers C_2 and C_{2a}
Tobramycin	Nebcin	*Streptomyces tenebrarius*	1967	Natural 3′-deoxy derivative of kanamycin B
Sisomicin[a]	Siseptin	*Micromonospora inyoensis*	1970	Dehydro analogue of gentamicin C1a
Dibekacin[a,b]		*Streptomyces kanamyceticus*	1971	Dideoxy derivative of kanamycin B
Amikacin[b]	Amikin	*Streptomyces kanamyceticus*	1972	Semisynthetic derivative of kanamycin A
Netilmicin[b]	Netromycin	*Micromonospora inyoensis*	1975	*N*-Ethyl derivative of sisomicin
Isepamicin[a,b]		*Micromonospora purpurea*	1978	*I-N-S*-α-Hydroxy B amino propionyl derivative of gentamicin B
Plazomicin	Zemdri	*Micromonospora inyoensis*	2018	Semisynthetic derivative of sisomicin

[a]Approved for human use in countries other than the United States.
[b]Semisynthetic aminoglycosides.
Modified from Wright GD, Berghuis AM, Mobashery S. Aminoglycoside antibiotics: structures, functions, and resistance. In: Rosen BP, Mobashery S, eds. Resolving the Antibiotic Paradox: Progress in Understanding Drug Resistance and Development of New Antibiotics. *New York: Plenum; 1998.*

TABLE 25.2 Chemical Families, Names, and Worldwide Availability

FAMILY	MEMBERS	EXAMPLE TRADE NAME	AVAILABLE IN UNITED STATES	AVAILABLE OUTSIDE UNITED STATES
Streptomycin	Streptomycin	Streptomycin	Yes	Yes
Kanamycin	Amikacin	Amikin	Yes	Yes
	Arbekacin	Habekacin	No	Yes
	Dibekacin	Dikacine	No	Yes
	Kanamycin	Kantrex	Yes	Yes
	Tobramycin	Nebcin	Yes	Yes
Gentamicin	Gentamicin (C_1, C_{1a}, C_2, C_{2a})	Garamycin	Yes	Yes
	Isepamicin	Isepacine	No	Yes
	Netilmicin	Netromycin	No	Yes
	Sisomicin	Sisogen	No	Yes
	Plazomicin[a]	Zemdri	Yes	Yes
Neomycin	Framycetin	Soframycin	No	Yes
	Neomycin	Mycifradin, Neobiotic	Yes	Yes
	Paromomycin	Humatin	Yes	Yes
Spectinomycin[b]	Spectinomycin	Trobicin	No	Yes

[a]Approved by the US Food and Drug Administration but not available in United States.
[b]An aminocyclitol, no glycosidic bonds.

pH and reduced in media with an acidic pH.[17] The positively charged aminoglycosides bind to the negatively charged RNA backbone, cell wall lipopolysaccharide (LPS), cell membrane phospholipids, and other anionic molecules.[19]

Cationic aminoglycosides interact chemically with β-lactam antibiotics.[20–22] The reaction results in a nucleophilic opening of the β-lactam ring, with acylation of an amino group of the aminoglycoside and mutual loss of antibacterial activity. In vitro, gentamicin and tobramycin are inactivated with greater ease than netilmicin, amikacin, or isepamicin. The antipseudomonal penicillins (e.g., piperacillin) are the β-lactams most susceptible to the reaction. The reaction requires several hours in vitro, so the clinical importance is limited. In general, penicillins and aminoglycosides should not be mixed in the same solution before infusion, although a recent product reformulation does allow piperacillin-tazobactam coadministration with gentamicin at specific doses.[23] If patients with renal failure are given an aminoglycoside and an antipseudomonal penicillin concomitantly, there is a 10% to 20% reduction in the serum aminoglycoside concentration compared with the levels observed when each drug is administered alone.[24]

MECHANISMS OF ACTION

Both electrostatic interactions between positively charged aminoglycoside amino groups and negatively charged RNA phosphate groups, as well as hydrogen bonds between multiple amino and hydroxyl groups of both, contribute to production of a tightly bound complex that derails translation.[25] Deoxystreptamine rings I and II, conserved and sequence specific among most aminoglycosides, are essential for binding to the ribosomal decoding acceptance (A) site. Aminoglycoside antibiotics preferentially bind with high avidity to a region of highly conserved nucleotides at the A site[26–28] in the 16S reverse transfer RNA portion of the messenger RNA (mRNA) decoding region of the 30S subunit of prokaryotic ribosomes.[25,29] Aminoglycoside binding induces a conformational change in three adenine residues that reduces the fidelity of normal mRNA translation and translocation (Fig. 25.2),[29,30] leading to

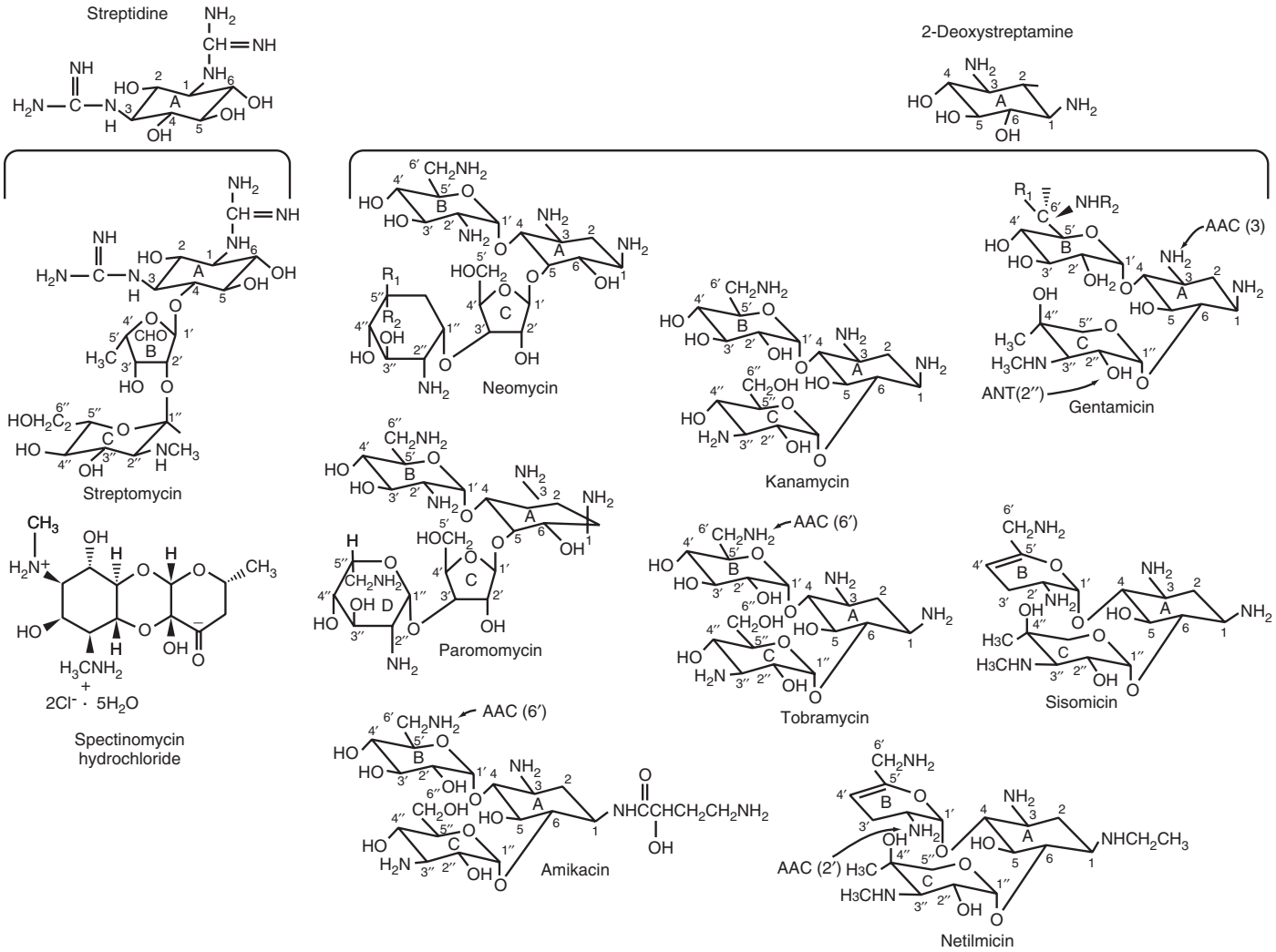

FIG. 25.1 Chemical structure of the aminoglycosides and spectinomycin. Neomycin contains approximately equal amounts of neomycin B (R_1 = H; R_2 = CH_2NH_2) and neomycin C (R_1 = CH_2NH_2; R_2 = H). Kanamycin is principally kanamycin A, as shown. Gentamicin is gentamicin C complex with roughly equal amounts of C_1 (R_1 = R_2 = CH_3), C_{1a} (R_1 = R_2 = H), and C_2 (R_1 = CH_3; R_2 = H). The sites of action of four inactivating enzymes are shown including three acetyltransferases—Aac(3′), Aac(2′), and Aac(6′)—and one adenyltransferase, Ant(2″).

the accumulation of truncated or nonfunctional proteins in bacteria. The respective nucleotide sequence differences between bacterial and human ribosomal subunits leads to lower affinity of aminoglycosides for the latter. In eukaryotic cytosolic ribosomes, adenosine is replaced by a guanosine within the A site, with a concomitant reduction in binding of aminoglycosides. The double-adenosine nucleotides in prokaryotic ribosomes create an internal bulge and a larger groove that allows access to the ribosomal binding site.[31] Avidity of binding varies with the aminoglycoside, depending on the number of amino groups and their state of protonation.[18]

Permeability of the polycationic aminoglycosides is enhanced in aerobic bacteria that use membrane-bound electron transporters. Initial electrostatic binding of aminoglycosides to the cell surface is followed by two energy-dependent uptake phases and binding to ribosomes.[32–34] In gram-negative bacteria, the cationic aminoglycosides rapidly bind to negatively charged residues in the LPS, polar heads of phospholipids, and anionic outer membrane proteins.[35–38] By competitively displacing cell wall magnesium ion (Mg^{2+}) and calcium ion (Ca^{2+}) bridges that normally link adjacent LPS molecules,[39,40] aminoglycosides result in a rearrangement of LPS, with subsequent bleeding of the outer membrane, formation of transient holes in the cell wall, and disruption of normal permeability function of the cell wall.[41]

After initial binding, aminoglycosides are transported across the bacterial cytoplasmic membrane by a slow energy-dependent phase, EDP-I, that transports the drug into the cytosol and then bind to the ribosome in a subsequent rapid energy-dependent phase, EDP-II.[32–34,38,42,43] The onset of bacterial killing is coincident with the transition from EDP-I to EDP-II.[33,34] Most bacterial cells manifest lethal injury after only 25% of the maximum EDP-II uptake.[43] The higher the external concentration of aminoglycoside, the quicker the intracellular drug concentration reaches a level necessary to trigger EDP-II uptake, which forecasts the death of the organism.[44]

Binding of aminoglycosides to prokaryotic ribosomes is a prerequisite for the drugs' antimicrobial activity. However, the exact mechanisms of bactericidal activity remain unknown.[1,25] The binding to ribosomes is reversible, which usually results in a bacteriostatic rather than a bactericidal effect.[1] Ribosomal binding results in a measurable decrease in protein synthesis as a result of misreading of mRNA. Although bactericidal drugs stimulate hydroxyl radical formation in bacteria as a function of metabolism-related depletion of reduced nicotinamide adenine dinucleotide, destabilization of iron-sulfur clusters, and stimulation of the Fenton reaction,[45] killing by antibiotics appears to be unrelated to reactive oxygen species.[46,47]

The mechanisms of the intracellular accumulation of high concentrations of drug and of cell death are unclear. High intracellular concentrations may result from aminoglycoside closure of voltage-gated channels, with subsequent trapping of drug.[48] Accumulation of large concentrations of aminoglycoside inside bacterial cells results in binding

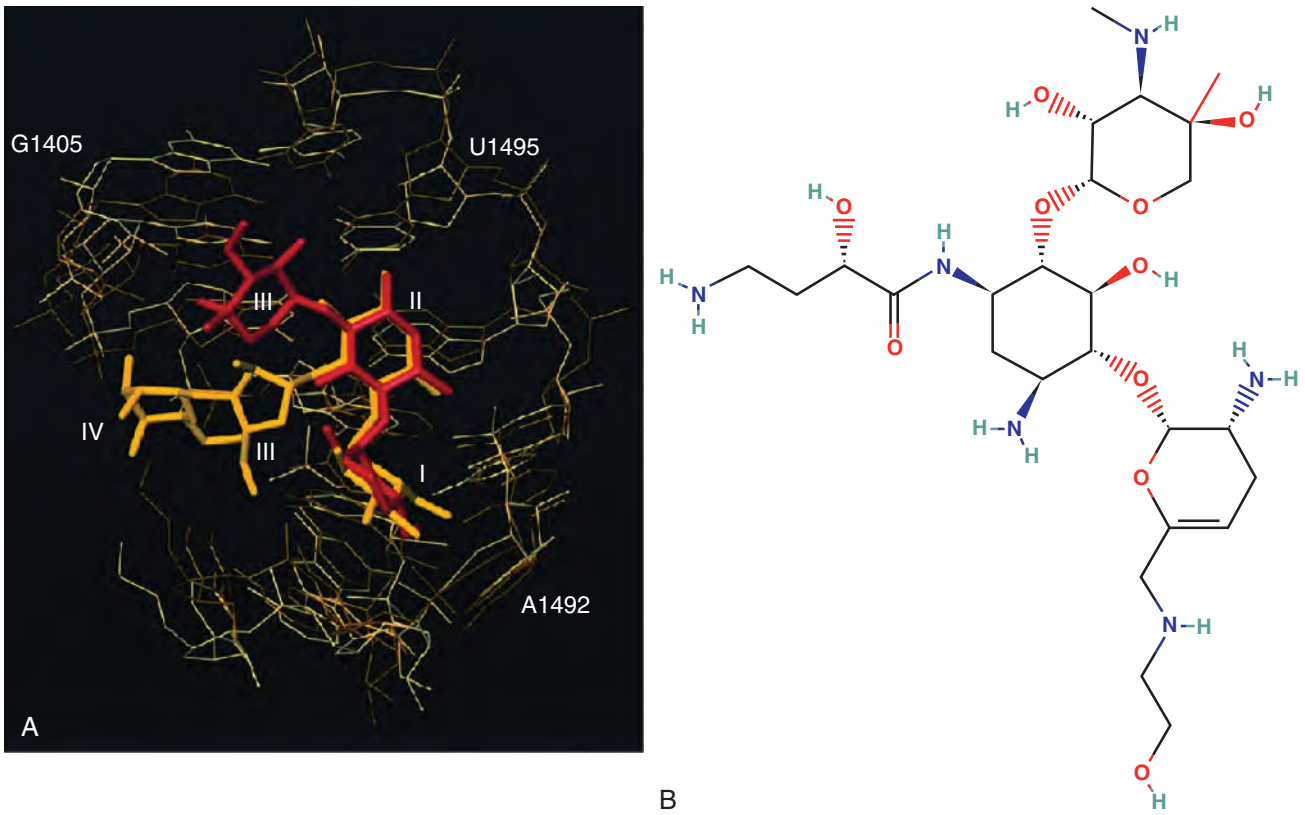

FIG. 25.2 (A) Three-dimensional structures of the aminoglycoside antibiotics paromomycin *(yellow)* and gentamicin C_{1a} *(red)* bound to different sections of the *Escherichia coli* 16S ribosomal RNA (shown in *light tan* and *dark tan*, respectively). Rings I and II of the two drugs, which are required for antibiotic activity, bind in the same mode in both complexes; the additional rings (III and IV in paromomycin and III in gentamicin C_{1a}), which are less important for drug activity, make diverse contacts with the RNA. (B) Structure of the aminoglycoside antibiotic plazomicin, newly approved by the US Food and Drug Administration. *(A courtesy Joseph D. Puglisi, Director, Stanford Magnetic Resonance Laboratory, Stanford University School of Medicine. B from Plazomicin. PubChem: Open Chemistry Database.* https://pubchem.ncbi.nlm.nih.gov/compound/Plazomicin#section=2D-Structure.*)*

to ribosomes with mistranslation of mRNA yielding abnormal proteins, loss of cell membrane integrity with efflux of intracellular ions, and inhibition of DNA replication, in addition to stimulating hydroxyl radical formation.[1,45]

The aminoglycosides have a variety of other biologic activities that are the subjects of ongoing study. Approximately 1800 genetic diseases (e.g., cystic fibrosis [CF], Duchenne muscular dystrophy, Hurler syndrome, nephrogenic diabetes insipidus) arise, in part, from base pair insertions, deletions, or substitutions that produce premature stop codons, resulting in production of incorrectly truncated, nonfunctional proteins.[49] Aminoglycosides can suppress premature stop codons and restore physiologically active amounts of functional protein.[50–58] The mechanism of the suppression of the stop codons is under study; uracil and cytosine nucleotides are major determinants of optimal gentamicin-induced readthrough.[59]

MECHANISMS OF RESISTANCE

Bacterial resistance to aminoglycosides results from some combination of the following three mechanisms: (1) reduction of intracellular aminoglycoside accumulation resulting from bacterial membrane alterations that reduce uptake or active efflux systems or both; (2) decreased aminoglycoside binding by mutation or methylation of the 16S ribosomal RNA (rRNA) binding site; and (3) enzymatic deactivation of aminoglycosides by *N*-acetylation, *O*-nucleotidation, or *O*-phosphorylation.[60–67] Aminoglycosides also induce bacterial biofilm formation, with associated bacterial cell wall surface adhesiveness. Biofilm formation is a concern in the treatment of chronic infections, especially infections with foreign bodies.[68] In addition, genomic studies in *Pseudomonas aeruginosa* have suggested other novel mechanisms of resistance.[69,70] As aminoglycosides require an active electron transport chain to generate an electrical potential difference across the membrane, anaerobic bacteria are intrinsically resistant to aminoglycosides.

Low-level aminoglycoside resistance attributed to impaired cell wall permeability may be the result of drug efflux mechanisms. Multidrug (including aminoglycoside) efflux pumps include adenosine triphosphate–dependent active pumps.[25] Constitutive expression results in intrinsic low-level resistance; overexpression of these transporters may result from regulatory gene mutations or increased antibiotic substrate concentration. Examples include the resistance nodulation cell division–type superfamily in *P. aeruginosa* and the major facilitator superfamily in *Escherichia coli*.[25,65] Activation of the MexXY efflux pump also appears to explain adaptive resistance, defined as transient resistance to aminoglycosides that follows the rapid, early, concentration-dependent killing of susceptible bacteria.[36,62] The refractory state lasts beyond the postantibiotic effective period into the time of regrowth. Adaptive resistance has been documented in vitro in animal models and in patients with CF,[63,71,72] where the predominant identified mechanism of aminoglycoside resistance is efflux by the MexXY-OprM system.[25,73,74] Exposure of susceptible bacteria to aminoglycosides can select a second type of drug resistance. A subpopulation results from small colony variants with deficient energy-dependent uptake of aminoglycosides and may result in clinical treatment failure.[75]

For most bacteria, the least common mechanism involves alteration of the 16S ribosomal target of aminoglycosides. However, the best known example is resistance of *Mycobacterium tuberculosis* to streptomycin as a result of point mutations in ribosomal protein S12 and in the 16S rRNA. Resistance of *Mycobacterium abscessus* and *Mycobacterium chelonae* to amikacin is the result of a 16S rRNA point mutation. Methylating enzymes that modify the 16S rRNA and decrease drug-binding affinity, mostly located on transposons within transferable plasmids, have been described in a growing number of aminoglycoside-resistant clinical isolates worldwide.[67,76–81]

The most common cause of aminoglycoside resistance is deactivation by specific enzymes derived from bacterial genes originally encoding enzymes involved in normal cellular metabolism of both gram-positive and gram-negative bacterial pathogens.[1,25] Examples of sites of enzyme activity are shown in Fig. 25.1. Enzyme modification results in loss of antibacterial activity.

Three covalent modifications of aminoglycosides are recognized: *N*-acetyltransferases (AAC), *O*-nucleotidyltransferases (ANT), and *O*-phosphotransferases (APH).[1,82] The enzymatically modified drugs bind poorly to ribosomes and result in high levels of resistance. In addition, the aminoglycoside may bind directly to a modifying enzyme in lieu of the ribosomal target.[83]

Specific enzymes are categorized by a nomenclature published in 1993.[1,84] Each enzyme is described by its class (AAC, ANT, or APH), a number in parentheses signifying the location of modification of the drug, and a Roman numeral indicating a unique aminoglycoside resistance profile. Distinct genes resulting in identical resistance phenotypes are indicated by a lowercase letter after the Roman numeral. For example, Aac(6′)-Ia describes an acetylating enzyme that modifies aminoglycosides at the 6′ position (see Fig. 25.1); the resistance profile is the same as that of Aac(6′)-Ib, but the enzyme protein is unique. A summary of modifying enzymes and their profile, source, and phenotype is available elsewhere.[1]

Modifying enzyme genes are spread by plasmids or transposons, or both. Some are chromosomal. The plasmid-transposon genes can result in rapid spread of drug-resistant phenotypes both within and between bacterial species. The resistance genes in gram-negative pathogens are diverse. In gram-positive pathogens, resistance is limited to Aph(3′)-IIIa, Ant(6′), and a unique bifunctional enzyme known as Aac(6′)-Aph(2″). In gram-negative organisms, a complex pattern of *aac(6′)*-I genes, combined with *aac(3)* and *ant(2″)* and others, is observed. The presence of the enzyme results in high-level resistance of gram-positive cocci to all aminoglycosides except streptomycin. Similar genes have been described in amikacin-resistant gram-negative bacterial clinical isolates.[85,86]

All enterococci have intrinsic resistance to aminoglycosides, with minimal inhibitory concentrations (MICs) ranging from 4 to 256 μg/mL.[87] The resistance is attributed to the facultative anaerobic metabolism of enterococci, which reduces the transmembrane potential and thereby limits drug intake. Concomitant exposure of enterococci to a cell wall–active drug such as ampicillin or vancomycin facilitates access of aminoglycosides to their ribosomal target site and classic synergistic bactericidal activity.

Acquisition of genes that encode aminoglycoside-modifying enzymes leads to high-level aminoglycoside resistance and loss of synergistic activity with penicillins or vancomycin. At least nine genes have been described that mediate resistance to aminoglycoside synergism in enterococci.[88] The most important is the bifunctional gene *aac(6″)-Ie–aph(2″)-Ia,* which encodes the bifunctional enzyme Aac(6′)-Ie–Aph(2″)-Ia. A combination of resistance genes can result in failure of synergism with all aminoglycosides available in the United States. Arbekacin, a derivative of dibekacin, available only in Japan, has shown promising results in the presence of a variety of modifying enzymes,[88] as has plazomicin.

The current threshold for detection of high-level resistance to gentamicin in vitro is an MIC of 2000 μg/mL or greater[89]; for resistance to streptomycin, it is an MIC of 500 μg/mL or greater. There are species differences in susceptibility to aminoglycosides. The MIC of tobramycin against *Enterococcus faecium* ranges from 62 to 1000 μg/mL; there is no synergism with a cell wall–active drug. The difference is caused by an enzyme that modifies tobramycin, but not gentamicin.[90]

Surveillance of the in vitro susceptibility of Enterobacteriaceae and nonfermentative gram-negative bacilli demonstrates increasing resistance to aminoglycosides as well as other classes of antibacterial drugs. Because the multiclass resistance genetic elements are on mobile units such as transposons or plasmids, their continued spread is anticipated.[91] One or more of the mechanisms of aminoglycoside resistance (e.g., enzymatic, target methylation, efflux pumps) are present in multidrug-resistant gram-negative bacilli. As a result of rapidly changing patterns of resistance, only general statements are possible regarding the anticipated in vitro and in vivo spectrum of antibacterial activity of aminoglycosides.[92–98]

ANTIMICROBIAL ACTIVITY

Although marked regional and individual hospital differences exist for in vitro susceptibility patterns, most aerobic and facultative gram-negative bacilli, including Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp. in the United States, remain susceptible to gentamicin, tobramycin, and amikacin.[8] Plazomicin is less active against lactose-nonfermenting gram-negative bacteria than against Enterobacteriaceae.[99] High rates (50%–60%) of cephalosporin and fluoroquinolone resistance are noted in aminoglycoside-nonsusceptible isolates.[13,67] *Yersinia pestis* is inhibited by streptomycin, and *Francisella tularensis* is inhibited by both streptomycin and gentamicin. The aminoglycosides show no inhibitory activity against *Stenotrophomonas maltophilia* or *Burkholderia (Pseudomonas) cepacia*. Among gram-positive aerobic bacteria, methicillin-sensitive *Staphylococcus aureus* is susceptible, and methicillin-resistant *S. aureus* isolates are resistant. All streptococci, including *Streptococcus pneumoniae*, are resistant. Because the aminoglycosides require aerobic metabolism to exert an antibacterial effect, it is not surprising that all the anaerobic bacteria are resistant to aminoglycosides.

There are some minor differences in relative degrees of in vitro potency of aminoglycosides. For strains of *S. aureus,* gentamicin and netilmicin show the most potency. The MIC or minimal bactericidal concentration of gentamicin against *Serratia* spp. is consistently twofold lower than that of the other aminoglycosides, and the MIC or minimal bactericidal concentration of tobramycin against *P. aeruginosa* is also consistently twofold lower than that of the other aminoglycosides. This increased potency increases both the peak/MIC and 24-hour area under the curve (AUC)/MIC ratios. Although tobramycin is more active in animal models of pneumonia, to date, no clinical efficacy data have been presented that parallel these in vitro differences. Even though amikacin MICs are generally higher against Enterobacteriaceae than gentamicin, amikacin remains active against most (>80%) strains as well as many *P. aeruginosa* strains that have acquired both gentamicin and tobramycin resistance.[17,100–102] Plazomicin is generally not inactivated by common aminoglycoside-modifying enzymes; however, 16S RNA methyltransferases render it and all aminoglycosides inactive. 16S RNA methyltransferases are currently found in <0.1% of Enterobacteriaceae in the United States.[67,103]

Aminoglycosides have in vitro activity against *Haemophilus* spp. and *Legionella* spp. but are not used clinically for infections with these organisms. Legionellae are intracellular pathogens, and the intracellular antimicrobial activity of the aminoglycosides is hampered by their low concentration in the acidic lysosomal compartment.[104] Nonetheless, aminoglycosides are used successfully in the treatment of other intracellular infections such as brucellosis, chronic forms of bartonellosis, tuberculosis, tularemia, and yersiniosis.[104–106] Aminoglycosides in combination with other drugs have been used successfully to treat infections with staphylococci, streptococci, enterococci, *Listeria,* and mycobacteria. Susceptibility of mycobacteria varies with the species. Streptomycin is the most potent aminoglycoside in vitro against *M. tuberculosis,* whereas amikacin is the most active against *Mycobacterium avium-intracellulare* complex.

The aminoglycoside paromomycin is too toxic for parenteral administration. Because the drug is not absorbed from the intestinal tract, it can be used safely as an alternative therapy for infection caused by *Entamoeba histolytica* as well as ulcerative *Leishmania major*.[105,107] Spectinomycin was an alternative agent used intramuscularly in the treatment of *N. gonorrhoeae,*[105] but it is no longer distributed in the United States.

Urine is known to partially inhibit the activity of aminoglycosides against urinary tract pathogens. Inhibition is believed to result from the low pH and high osmolality caused by the high salt and glucose concentrations. In addition, present data support the hypothesis that betaines, normally found in urine, permit the expression of increased aminoglycoside resistance.[108]

Three characteristics describe aminoglycoside antibacterial activity: concentration-dependent killing, the presence of a postantibiotic effect (PAE), and synergism with other drugs.[109] Aminoglycosides are rapidly bactericidal, and their rate of bacterial killing increases as the antibiotic concentration is increased, regardless of the inoculum.[3] Exposure of both gram-positive and gram-negative organisms to less frequent, higher

doses with in vitro pharmacokinetic models resulted in more and faster killing initially, followed by regrowth of resistant mutants and very similar 24-hour results, compared with more frequent dosing regimens.[110,111] Further studies indicated that emergence of resistance could be prevented with peak/MIC ratios greater than 8.[112]

In thigh infections of neutropenic mice, the rate of killing increased with increasing mg/kg doses over the first few hours, whereas regrowth was suppressed for several hours despite aminoglycoside levels less than the MIC.[113] The duration of this postexposure growth suppression, or PAE, also increases with higher doses.[114,115]

The PAE represents suppression of bacterial growth after short antimicrobial exposure.[114,115] In vitro, the tobramycin-induced PAE against *E. coli* correlated with inhibition of protein synthesis, but not of DNA or RNA synthesis.[116] An aminoglycoside PAE can be demonstrated after incubation with *S. aureus* but not after contact with *S. pneumoniae*.[114] Inoculum size, oxygenation, and pH of the medium affect the duration of in vitro PAE.[114,115,117] For the aerobic or facultative gram-negative rods tested, combinations with β-lactams other than imipenem result in the same PAE as that of the aminoglycoside alone.[114,118] Rifampin was associated with synergistic enhancement of the PAE induced in *P. aeruginosa* by tobramycin.[115,119]

The in vivo PAE of aminoglycosides has been studied in at least five animal models.[113,114,120] In neutropenic mouse thighs infected with 15 clinical isolates of Enterobacteriaceae, the in vivo PAE after gentamicin therapy varied from 1.4 to 6.9 hours. In the same model infected with *P. aeruginosa,* increasing the dose of tobramycin fivefold increased the PAE from 2.2 to 7.3 hours.[113] The in vivo PAE is prolonged further in renally impaired or nonneutropenic mice and larger animals.[121]

Aminoglycoside combinations have been widely studied in vitro and for many years have been used in combination with other antibiotics to enhance bacterial killing and improve clinical efficacy. Synergy, a more than additive effect, has been shown in multiple time-kill curve experiments between an aminoglycoside and a cell wall–active antimicrobial (e.g., penicillin, cephalosporin, monobactam, carbapenem, glycopeptide).[2,109,122] The mechanism of aminoglycoside synergistic activity may not be the same for all target organisms. Enhanced aminoglycoside uptake in the presence of a cell wall–active drug has been demonstrated with enterococci, viridans streptococci, *S. aureus,* and *P. aeruginosa*.[109] No combination of aminoglycoside and cell wall–active drug is indicated as effective for methicillin-resistant *S. aureus*. In vitro synergism against *P. aeruginosa* and Enterobacteriaceae[109,123] does not appear to translate into all clinical situations.[124] Of equal importance, the bactericidal activity of aminoglycosides can be antagonized by bacteriostatic agents such as chloramphenicol and tetracycline.[109] The mechanism is unclear. Possibilities include inhibition of the energy-dependent uptake of aminoglycosides and interference with movement of the ribosome along mRNA. Provocative modeling work suggests new innovative combinations may likewise prove synergistic.[125]

Aminoglycoside combinations have been evaluated in animal models of endocarditis, meningitis, pneumonia, peritonitis-bacteremia, pyelonephritis, osteomyelitis, myositis (mouse thigh), and subcutaneous infection with or without a foreign body, as well as additional conditions.[109,115,126–135] In general, if the organism is susceptible to both the aminoglycoside and the companion drug, antibacterial activity is enhanced; virtually all studies showing effectiveness of combined therapy used a cell wall–active drug (β-lactam or glycopeptide) with the aminoglycoside.

An aminoglycoside as part of combination therapy may prevent or delay the emergence of bacteria resistant to either the aminoglycoside or the companion drug. In a series of studies, aminoglycosides were shown to reduce, but not to fully prevent, the emergence of quinolone-resistant strains of Enterobacteriaceae or *P. aeruginosa* in a murine model of peritonitis.[136–138] The concomitant use of an active β-lactam appears to prevent the emergence of gentamicin-resistant subpopulations in neutropenic animals.[139]

Treatment of infected animals with gentamicin markedly reduced mortality but had virtually no influence on the incidence of abscess formation.[140–142] Treatment with clindamycin or metronidazole reduced the incidence of abscess formation but had no effect on peritonitis-bacteremia or lethality.[143] Combination therapy reduced both acute mortality and late abscess formation despite conditions adversely affecting aminoglycoside activity such as low pH, at low oxygen tension, and in the presence of drug-binding purulent debris.[17,19,144]

Data from infected animals and analysis of clinical trial data support the correlation between high peak levels, increased dose, and antibacterial efficacy.[131,145–148] Dose fractionation studies reduce the interdependence among the various pharmacokinetic parameters in small rodents with rapid aminoglycoside clearance. In these models, the therapeutic efficacy of aminoglycosides correlates with the peak serum concentration and the area under the concentration versus time curve (i.e., AUC) over time.[131,132] A compilation of clinical trials involving aminoglycosides for gram-negative bacillary infections has shown that peak/MIC and 24-hour AUC/MIC ratios predicted outcome.[147,149,150] Clinical efficacy increased from 55% for a peak/MIC ratio less than or equal to 2 to 90% for a ratio greater than 8 when four different aminoglycosides all were administered by identical traditional every-8-hour dosing regimens. Efficacy improved from 47% for tobramycin AUC/MIC ratios less than 110 to 80% for ratios greater than 110. Both peak greater than or equal to 10 and AUC greater than 150 correlated with rapidity of fever and leukocytosis resolution in gram-negative pneumonia. These favorable results applied only to organisms with MICs less than or equal to 0.5 μg/mL. Current maximal dosing regimens of 7 mg/kg routinely achieve peak/MIC ratios greater than or equal to 10 for bacteria with MICs less than or equal to 1 μg/mL, but Clinical and Laboratory Standards Institute susceptibility breakpoints are 4 μg/mL. Synergistic activity with β-lactams may allow adequate coverage for those increasing numbers of organisms with MICs 2 to 4 μg/mL.[151,152]

More than 55 clinical trials, including more than 30 prospective randomized trials and 9 formal meta-analyses, have compared aminoglycoside once-daily administration with traditional 8- or 12-hour administration, showing equivalency or superiority of once-daily regimens. In largely prospective fashion, more than 6500 mostly nonneutropenic adult patients have received amikacin, gentamicin, netilmicin, or tobramycin for periods of 7 to 14 days.[153–199] Comparable antimicrobial efficacy and toxicity were recorded for a broad range of infections, including pneumonia, intraabdominal infections, gram-negative sepsis, febrile neutropenia, pelvic inflammatory disease, and urinary tract infections. Populations studied included elderly patients,[169,182] febrile neutropenic patients,[a] critically ill patients,[156,164,182,198] and patients with variable levels of renal insufficiency.[162,182,193,195]

Five meta-analyses have shown statistically significantly improved clinical outcomes, and three have shown significantly lower nephrotoxicity, when aminoglycosides were dosed once daily. Likewise, equivalence or a trend toward lower ototoxicity was shown with once-daily administration. Among trials identifying a time to onset of toxicity, once-daily dosing delayed nephrotoxicity compared with 8-hour dosing until total duration approached 10 to 14 days, when the incidence became similar in both groups. Two trials comparing once-daily with twice-daily dosing of amikacin, gentamicin, and tobramycin showed that the incidence of nephrotoxicity was lower with once-daily dosing when using short courses of therapy and was delayed more for an equivalent total amount of standard therapy drug.[200,201]

Once-daily dosing regimens have similar or slightly better clinical efficacy than twice-daily or three times–daily regimens. Plazomicin has been developed solely for a once-daily dosing regimen. If current recommendations limiting duration to only 5 to 6 days[200–202] are followed, once-daily dosing can also delay the onset of nephrotoxicity. For treatment regimens lasting longer than 5 to 6 days, aminoglycoside dosing by individualized pharmacokinetic modeling may result in less nephrotoxicity.[203] Consideration should also be given to morning administration of aminoglycosides to minimize nephrotoxicity, when food intake and higher urinary pH in diurnally active humans may reduce renal toxicity.[204]

An overview[194] of the large, published, extensively analyzed experience in patients indicates that once-daily aminoglycoside administration

- Is as efficacious as the traditional multiple-dose method (see later discussion of exceptions).
- May lower, but not eliminate, the risk of drug-induced nephrotoxicity and ototoxicity.

[a]References 155, 170, 177, 182, 193, 197.

- Is simpler (less human error–prone), less time-consuming, and more cost-effective than multiple-dose regimens.
- Is not universally advocated in patients with enterococcal endocarditis.[205,206]
- Needs further study in selected populations of patients, such as pregnant women, patients with CF (see "Cystic Fibrosis"), patients with meningitis caused by aerobic gram-negative bacilli, and patients with osteomyelitis
- Does not worsen neuromuscular function even in critically ill, ventilated patients; nonetheless, rapid intravenous infusion should be avoided.[207]

At the present time, once-daily aminoglycoside administration is as efficacious as traditional multiple-dose regimens and may reduce the risk of nephrotoxicity, but further study in selected populations is needed.

CLINICAL PHARMACOLOGY

Aminoglycosides are generally administered intravenously over a 30- to 60-minute period. However, outpatient slow push infusion over 3 to 5 minutes has been safely administered in more than 5000 patients over 15 years in one center.[208] Aminoglycoside given intramuscularly is absorbed completely, with maximal serum levels achieved 30 to 120 minutes after administration.[209] Absorption may be delayed in elderly patients and patients with compromised renal function, hypotension, or impaired tissue perfusion. Aminoglycosides are minimally absorbed from the gastrointestinal tract.[210] Nonetheless, instances of deafness have resulted from administration of oral neomycin to patients with hepatic encephalopathy and impaired renal function.[211] Also, increased absorption in the presence of concomitant inflammatory bowel disease is of theoretical concern. In contrast, patients with acquired immunodeficiency syndrome and severe cryptosporidiosis have ingested large amounts of paromomycin over protracted periods without evidence of toxicity. Other exposures may lead to systemic toxicity. Topical application of aminoglycoside on inflamed skin leads to no or minimal absorption. However, patients with extensive burns or other severe dermal injury may absorb a drug and be at risk for toxicity.[212] Aminoglycosides can be instilled into the pleural space or the peritoneal cavity; absorption is rapid, with resultant serum concentrations proportionate to the concentration of drug instilled. The use of aminoglycosides in abdominal irrigation solutions is not recommended because rapid absorption with subsequent neuromuscular blockade has been reported.[213] In contrast, aminoglycosides have been administered as a bladder irrigant, as an aerosol, and by direct instillation into the lumbar sac or lateral ventricles without evidence of detectable concentrations in the blood.[214–216] Inhalation has also been used, especially in patients with CF.[217–223]

As anticipated for drugs with a low level of protein binding (approximately 10%–20%) and a high level of solubility in water, the aminoglycosides are distributed freely in the vascular space and relatively freely in the interstitial spaces of most tissues.[224] Significant interpatient variability in aminoglycoside volume of distribution has been demonstrated, as well as intrapatient variation during therapy.[225,226] In the absence of disease or infection, the volume of distribution mirrors that of the extracellular fluid compartment—0.2 to 0.3 L/kg.[227] The volume of distribution increases in edematous states including ascites, in patients with burns, in patients with CF, and in some severe infections when conditions may vary from hour to hour in critically ill patients.[228] The volume of distribution increases less than expected or actually decreases in obese individuals.[229] Because of their size, polycationic charge, and lipid insolubility, aminoglycosides cross biologic membranes poorly, with the exception of renal tubular cells and perhaps inner ear cells that appear to have an inherent transport mechanism. The cells of the renal proximal convoluted tubule can concentrate aminoglycosides to levels that exceed those of plasma or interstitial fluid.[230]

Adequate antibiotic concentrations are achieved in most body fluids.[231] Aminoglycosides enter synovial fluid easily, with subsequent concentrations only slightly less than simultaneous serum concentrations.[232] Parenteral aminoglycoside administration results in low concentrations of active drug in bronchial secretions.[216] Penetration into epithelial lining fluid ranges from 32% to 54% of serum concentrations.[233,234] Much higher concentrations can be achieved by aerosol administration.[218] Diffusion is slower in bile, feces, prostatic fluid, and amniotic fluid.[235–237]

Aminoglycosides traverse the blood–cerebrospinal fluid and blood-brain barriers poorly[238] but do cross the placenta and achieve fetal serum concentrations 21% to 37% of maternal concentrations.[237] Intraventricular administration results in high concentrations in both ventricular and spinal fluid.[238–241] Therefore the intraventricular route is recommended for meningitis caused by aerobic gram-negative bacilli in adults in the rare cases in which this therapy is necessary. However, in newborns, intraventricular aminoglycoside is no more effective and perhaps more toxic than the drug given intravenously. Aminoglycoside penetration into the tissues of the eye is poor; neither systemic nor subconjunctival administration in single doses produces reliable levels in the vitreous humor of humans.[242–245] Direct intravitreal injection is recommended for the treatment of endophthalmitis.

Urine concentrations of aminoglycosides exceed peak plasma levels 25- to 100-fold within 1 hour after drug administration.[246,247] Because of renal tubular cell absorption and subsequent release, urine concentrations remain above therapeutic levels for several days after a single dose, even in severe renal impairment. After termination of a multiple-dose regimen, urine levels remain above therapeutic levels for days, with a terminal half-life of 48 to 200 hours.[247–249]

Aminoglycosides are primarily eliminated unchanged by the kidney via glomerular filtration. Less than 1% is eliminated in the feces, and 1% is eliminated in saliva.[250] Aminoglycosides can be removed by dialysis, leading to unpredictable clearance depending on the specific modality and dialysis membrane capacity.[251] With normal renal function in adults, more than 90% of an administered dose is recovered in urine unchanged during the first 24 hours.[250,252] The remainder is slowly recycled to the tubular lumen, with a tissue half-life of 30 to 700 hours,[252,253] creating a multicompartmental elimination profile.[254,255]

The pharmacokinetics of aminoglycosides in clinical use are very similar, even though interpatient variability is broad and associated with body weight, body composition, and renal function as noted earlier. Typical expected aminoglycoside pharmacokinetic parameter values are summarized in Table 25.3. Peak serum concentrations of gentamicin, netilmicin, and tobramycin after a dose of 7 mg/kg infused over 30 minutes range from 15 to 20 μg/mL and yield an AUC of 70 to 100 mg · h/L. An amikacin dose of 15 mg/kg similarly infused produces peak levels of 41 to 49 μg/mL and an AUC of 110 to 145 mg · h/L.[2] In patients with renal impairment, peak concentrations are higher, and AUCs are larger. Suggested initial dosing regimens for typical aminoglycosides in clinical use are listed in Table 25.4. One caveat to proper interpretation of these published nomogram concentrations is that the "peaks" were likely obtained before the end of distribution, whereas pharmacodynamic data use actual postdistribution peaks. Blind use of a 7-mg/kg dose may not achieve peaks related to expected pharmacodynamic outcomes.[256] Disease states that result in significant loss of muscle mass are associated with low serum creatinine values. In such patients the Cockcroft-Gault formula may seriously overestimate the glomerular clearance of aminoglycosides.[257] For this reason, it has been suggested that the minimum value for subcutaneous administration used in the formula be 0.8 μg/mL.[258] However, a study in elderly patients showed that such a practice significantly underestimated creatinine clearance (CrCl) and recommended that the practice should be avoided.[259] The US Food and Drug Administration (FDA), several decades before pharmacodynamic research into dose optimization, approved gentamicin and tobramycin for up to 1.7 mg/kg per dose, three doses per day, for a total daily dose of 5.1 mg/kg.[260] For netilmicin the total daily dose is 6.0 mg/kg, and for amikacin total daily dose is 15 mg/kg. In one clinical study that included a high percentage of critically ill patients the peak serum gentamicin concentration after the first dose of 5.1 mg/kg was less than 16 μg/mL in 48% of the patients.[260] Therefore in critically ill patients, it is reasonable to give an initial dose of 7.0 mg/kg.[198] Extended-interval dosing is the norm today, used in 75% of all acute care hospitals.[261] No controlled studies have compared 5 mg/kg/day versus 7 mg/kg/day of gentamicin or tobramycin, but clinical experience with 7 mg/kg/day is substantial.[192,193] With the exception of patients with CF, the clinical use of single doses of amikacin or netilmicin exceeding the licensed total daily dose has not been reported. To date, FDA-approved labeling on therapeutic drug monitoring kits for aminoglycosides suggests "normal ranges" of serum concentrations are achievable with traditional dosing of three

times daily rather than the higher, more effective serum concentrations now achievable with extended-interval dosing.

Various dialysis modalities clear differing amounts of aminoglycosides, roughly one-half of circulating aminoglycoside per hemodialysis period, depending on the characteristics of the dialysis membrane, duration of dialysis, the patient's blood pressure during dialysis, and other variables. Depending on variables related to both the patient and the filter, continuous hemofiltration results in the equivalent of a CrCl of 10 to 50 mL/minute.[262,263] For patients undergoing continuous ambulatory peritoneal dialysis who have a systemic infection and are receiving an intravenous dose of aminoglycoside every 2 to 3 days, it is necessary to give small daily intravenous supplements to replace the drug lost in the dialysate or dosed based on serum concentrations (www.pdiconnect.com/content/30/4/393.full.pdf+html). For patients on hemodialysis, a traditional dose is given every 48 to 72 hours, and on the day of hemodialysis an additional one-half of the full dose is given (if the traditional dose was administered prior to dialysis) after dialysis in order to replace drug that was removed by the dialysis or simply dosed after dialysis. Because of individual variability, serum levels should be measured.[264–266]

TABLE 25.3 Typical Pharmacokinetic Parameters for Amikacin, Gentamicin, Netilmicin, and Tobramycin in Adults With Normal Renal Function

PARAMETER	MEAN (± SED) OR RANGE
Clearance, mL/min/kg	
Creatinine ≤1.5	1.33 (0.61)
Creatinine >1.5	0.53 (0.35)
CrCl ≥100	1.51 (0.63)
Volume of distribution, L/kg	
Dehydration	0.07–0.15
Euvolemic	0.15–0.25
Expanded ECF	0.35–0.70
Half-life, h	
Creatinine <1.5	0.15–15
CrCl ≥100	0.5–7.6
Age <30 y	0.5–3
Age >30 y	1.5–15
Urinary excretion	85%–95%

CrCl, Creatinine clearance; *ECF,* extracellular fluid; *SED,* standard error of the difference.
Modified from Schentag JJ, Meagher AK, Jelliffe RW. Aminoglycosides. In: Burton ME, Shaw LM, Schentag JJ, et al, eds. Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring. *Philadelphia: Lippincott Williams & Wilkins; 2006.*

Dosing for morbidly obese patients is generally based on excess body weight multiplied by 0.4 plus ideal body weight. More recent work indicates that lean body weight permits simplified aminoglycoside dosing across all weight strata, with clearance best predicted by the Chronic Kidney Disease Epidemiology Collaboration equation.[267–269] However, the best clinical descriptor of renal function for pharmacokinetic modeling in elderly patients is the Cockcroft-Gault–based model.[270] Monitoring early peak concentration (and another to estimate AUC) may assist in optimizing aminoglycoside efficacy.[9,151] It is unclear whether every patient administered an aminoglycoside requires an individual pharmacokinetic evaluation,[271] but individualized dosing is essential in a critically ill patient with altered volume of distribution of drug and unstable renal function. Use of new Bayesian analysis in routine clinical care holds promise.[272,273] Overall, individualized dosing results in greater efficacy and reduced toxicity compared with the nomogram approach.[259,270,274]

Typically, two concentrations in the postdistribution phase (>1 hour after administration, separated by >1.5 half-lives) are used. Trough levels should be below the limit of detection.

With the exception of the aminocyclitol spectinomycin, aminoglycoside antibiotics share the potential for causing injury to the renal proximal convoluted tubules, damage to the cochlea or vestibular apparatus or both, and neuromuscular blockade (Table 25.5). The inherent toxicity and relative toxic potential of the aminoglycosides correlate with their positive electrical charge at physiologic pH.[14]

Also important are untoward effects that are encountered rarely. Hypersensitivity reactions and drug fever are uncommon, and the aminoglycosides do not provoke inflammation. Hence phlebitis at intravenous infusion sites is rare; intramuscular injection sites do not become painful; instillation into the pleural space, abdominal cavity, or cerebrospinal fluid causes no irritation; and incorporation of an aminoglycoside into methyl methacrylate prosthetic joint cement is well tolerated over protracted periods. The aminoglycosides are not hepatotoxic, do not induce photosensitivity, and have no identified adverse influence on hematopoiesis or the coagulation cascade.

Nephrotoxicity

Experimental Nephrotoxicity

The precise mechanisms of aminoglycoside-induced injury to renal proximal tubular cells remain incompletely understood. There are as yet unidentified genetic factors and major differences in susceptibility to nephrotoxicity between animal species and between inbred strains of a specific animal.[275]

Aminoglycosides initially bind to an endocytotic receptor, megalin,[276,277] important in the endocytotic uptake of proteins in the renal proximal tubule.[276–278] In megalin receptor knockout mice, there

TABLE 25.4 Suggested Dosing Regimens for Adults

ESTIMATED CREATININE CLEARANCE (mL/min)	DOSE (mg/kg)			DOSING INTERVAL (h)
	Gentamicin, Netilmicin, Tobramycin	Plazomicin	Amikacin	
100	7	15	20	24
90	7	15	20	24
80	7	15	20	24
70	5	15	15	24
60	5	15	15	24
50	4	10	12	24
40	4	10	12	24
30	5	10	15	48
20	4	10	12	48
10	3	10	10	48
<10	2.5	N/A	7.5	48

N/A, Not available.
Modified from Gilbert DN, Bennett WM. Use of antimicrobial agents in renal failure. Infect Dis Clin North Am. *1989;3:517–531.*

TABLE 25.5 Estimated Frequency of Serious Clinical Adverse Reactions After Administration of Aminoglycoside Antibiotics

ADVERSE REACTION	ESTIMATED USUAL FREQUENCY (%)	REFERENCES
Nephrotoxicity	5–15	252–262
Ototoxicity	2–14	
Cochlear	2–10	284–286
Vestibular	3–14	284,312,313
Neuromuscular blockade	Exceedingly rare	145,325

TABLE 25.6 Factors That Increase Risk for Aminoglycoside Nephrotoxicity

- Patient-related factors
  - Older patient
  - Preexisting renal disease
  - Female[214]
  - Male[260]
- Volume depletion, hypotension
- Hepatic dysfunction
- Aminoglycoside factors
  - Recent aminoglycoside therapy
  - Larger doses
  - Treatment for ≥3 days
  - Drug choice (e.g., gentamicin)[255]
  - Frequent dosing interval[128,268]
- Concomitant drugs
  - Vancomycin[277–279]
  - Amphotericin B
  - Furosemide
  - Clindamycin
  - Piperacillin
  - Cephalosporins?[263,274–276]
  - Methoxyflurane[282]
  - Foscarnet
- Intravenous radiocontrast agents

Data from references 215, 216, 253, and 260 and references cited in table.

was no renal uptake of aminoglycosides.[279] After binding to the anionic megalin in clathrin-coated pits,[276,280] the cationic aminoglycoside is transferred to endosomes, and the megalin is returned to the apical plasma membrane. A portion of drug-containing endosomes fuses with lysosomes, where the aminoglycosides inhibit lysosomal phospholipases, resulting in lysosomal whorl-like membrane changes that, because of their morphologic appearance, have been termed *myeloid bodies*.[276] Some aminoglycoside-containing endosomes move rapidly to the Golgi apparatus.[281] The time frame correlates with the observed rapid decrease in cellular protein synthesis after aminoglycoside exposure.[282–285]

In cells that internalize aminoglycosides, cellular necrosis occurs gradually, during which time a variety of abnormalities are demonstrable,[286–297] leading to activation of the apoptotic pathway with subsequent necrosis of the cells of the proximal tubules.[297] Initially, animals manifest nonoliguric renal failure.[298] After several days, there is a fall in glomerular filtration. The cells of the proximal tubule can regenerate with return of glomerular filtration. Regeneration occurs even if there is continued administration of the aminoglycoside.[299] In animals the regenerated tubular cells have a reduced capacity to take up aminoglycosides.

A hierarchy of nephrotoxic potential exists among the aminoglycosides.[300–302] Neomycin is the most toxic aminoglycoside,[303] and streptomycin is the least nephrotoxic, perhaps because the drug does not accumulate in the renal cortex.

Aminoglycoside uptake into the proximal renal tubular cell is saturable at clinically relevant concentrations, governed by Michaelis-Menten kinetics.[276] Thus for a given total daily dose of a specific aminoglycoside the magnitude of toxicity is greatest when the dose is divided into multiple small increments and least when it is given as a single daily dose.[301,304,305] In addition, age, sex, volume status, pH, and electrolyte balance all have been examined, with older age, dehydration, lower urinary pH, and electrolyte depletion associated with increased toxicity.[b] The impact of experimental liver disease or diabetes is unclear, but accumulated clinical data indicate that concomitant liver disease is a risk factor for nephrotoxicity.[318–322] Various drugs influence the severity of experimental aminoglycoside nephrotoxicity.[323–331] Vancomycin and the related drug teicoplanin amplify experimental aminoglycoside nephrotoxicity.[323–331] Extended-spectrum penicillins reduce the risk of kidney injury.[326,327] Polymers of aspartic acid dramatically reduce renal tubular injury despite the accumulation of very high renal concentrations of aminoglycoside.[332–341] Animal experiments with an aminoglycoside plus cephalothin, cefazolin, or cefamandole indicated either no effect or an attenuation of nephrotoxicity compared with an aminoglycoside plus placebo.[342] Fosfomycin may reduce aminoglycoside experimental nephrotoxicity by inhibiting gentamicin-induced lipid peroxidation.[343] In general, ascribing causation to a single factor in a multivariate interaction resulting in toxicity is not a statistically valid approach. In a clinical study, no identifiable risk factor alone or in combination reliably predicted nephrotoxicity.[344]

Clinical Nephrotoxicity

One factor in the nephrotoxicity of aminoglycosides is that they accumulate in the kidney, accounting for 40% of the total drug in the body,[255] and nearly 85% of this is located in the renal cortex. The reported incidence of nephrotoxicity ranges from 0% to 50%, with most reports in the 5% to 15% range (see Table 25.5).[345–352] The variability results from differences in the definition of nephrotoxicity, the frequency of testing, and the particular tests used to measure renal function and the clinical setting in which the drugs are administered. Minimal clinical differences were seen in a survey of clinical trials involving approximately 10,000 patients between 1975 and 1982.[345] Frequencies of nephrotoxicity averaged 14.0% for gentamicin, 12.9% for tobramycin, 9.4% for amikacin, and 8.7% for netilmicin. In prospective, randomized studies with definitions of nephrotoxicity that reflect a substantive decrement in the glomerular filtration rate (GFR) in seriously ill patients, the reported incidence varied between 5% and 10% of patients' courses.[347–352]

In studies of the etiology of acute renal failure, medication-induced renal injury is reported as a major cause. In an analysis of more than 2000 hospitalized patients, almost 100 experienced renal insufficiency, and seven episodes were attributed to aminoglycoside therapy.[353] In general the aminoglycoside-induced decrement in the GFR is small. Most patients have a nonoliguric fall in CrCl; progression to dialysis-dependent oliguric-anuric renal failure is rare. As in animal models, the tubular injury is reversible, and in a few patients, recovery of renal function has been documented despite continued administration of the aminoglycoside.[354]

Reported clinical risk factors for aminoglycoside nephrotoxicity can be grouped as being related to the patient, to the aminoglycoside, or to the influence of the selected concomitant drug (Table 25.6).[c] Factors identified in clinical trials include older age, preexisting renal or liver disease, shock, larger volume of distribution, location in intensive care unit, pneumonia, rapidly fatal prognosis, leukemia, longer duration of therapy, and concomitant vancomycin or other nephrotoxin. Female sex was identified as a risk factor in one study but was not confirmed in others.[308,345,350–352] Reported clinical studies with cephalosporins did not include an aminoglycoside-only group of patients, so it is not possible to ascertain the effect of cephalosporins on the risk of nephrotoxicity. The correlation of increased risk of toxicity with age and with preexisting renal disease may be misleading. It is unclear whether a risk exists when the dosing regimen is adjusted for a preexisting decrease in the GFR, and this was not a risk factor in several studies.[345,346,350] Hypotensive patients, especially patients with septic shock or sepsis syndrome, have an increased incidence of renal insufficiency. The role of aminoglycosides is unclear in that infection-induced low perfusion pressures, consumptive coagulopathy, cytokine-mediated endothelial damage, and other factors may be etiologic in the fall in GFR.[355,356] Liver disease was identified as

[b]References 66, 68–73, 75–90, 92–98, 100–102, 104–198, 200–204, 208–222, 224–272, 274–291, 306–317.

[c]References 308, 309, 345, 346, 350, 357, 358.

a risk factor in the retrospective analysis of two large clinical trials and was then validated in two additional prospective trials.[320,357]

Clinical trial data support the concept that several days of therapy are needed to cause nephrotoxicity of clinical consequence. In an observational study of patients treated with combination therapy, including an aminoglycoside for infective endocarditis, there was a 0.5% decrease per day in the estimated endogenous CrCl.[358] In contrast, accidental massive overdosage of 1 day or less has not resulted in acute tubular necrosis.[359,360]

The influence of concomitant drugs is difficult to interpret in patients with serious or complex disease states who are receiving many drugs. Nonetheless, most studies suggest an increased risk of a fall in GFR when other nephrotoxic drugs are administered concomitantly with aminoglycosides.[d] Three prospective studies, one of which was a double-blind study, found the combination of cephalothin plus aminoglycoside more nephrotoxic than the combination of a penicillin derivative plus an aminoglycoside.[361–363] Subsequent multiple logistic regression risk factor analysis identified a variety of cephalosporins as risk factors. These results are consistent with ceftazidime enhancement of gentamicin enzymuria in healthy volunteers.[364] Two studies evaluated concomitant vancomycin administration; one analysis included a control group that received only an aminoglycoside.[365,366] Both studies indicated that vancomycin was a risk factor. In febrile neutropenic patients administered gentamicin or tobramycin plus carbenicillin or ticarcillin, the reported incidence of nephrotoxicity was 2% to 6% compared with 10% to 15% or higher when the aminoglycoside was combined with other β-lactam antibiotics.[361,362,367] A risk factor analysis found an increased risk with concomitant piperacillin but not with carbenicillin or ticarcillin. The authors speculated that the lower sodium content of piperacillin might explain the difference.[327]

Ototoxicity

Aminoglycoside antibiotics can cause cochlear and vestibular damage in experimental animals and humans.[372] Streptomycin-induced hearing loss and dizziness were included in the first clinical report of the drug's efficacy.[373] Overt ototoxicity was noted in 2% to 10% of patients in early clinical experience.[374,375] Ototoxicity is of particular concern because it is usually irreversible and can appear after the end of treatment; moreover, repeated exposure engenders cumulative risk.[376] A patient may suffer only cochlear damage or only vestibular damage, but in general the predominant lesion is vestibular.[377] Rarely, both organs are injured. It is unusual to have both ototoxicity and nephrotoxicity in the same patient.

Cochlear Toxicity

Few recipients of aminoglycoside therapy complain of hearing loss, and yet the reported incidence is as high as 62% when asymptomatic high-frequency audiograms are performed repeatedly.[378] The overall incidence has been reported to be between 3% and 14%.[379]

Normal sound perception extends to frequencies of 20 kHz; perception of human speech requires sound detection in the range of 0.3 to 3 kHz. A loss of hearing threshold of 25 to 30 dB is necessary before the patient is aware of the deficit. A commonly used definition for drug-induced ototoxicity is an increase in auditory threshold of 15 dB or greater at any of two or more frequencies.[376]

Controlled data on cochlear toxicity are sparse. In a series of prospective clinical studies that examined the efficacy and toxicity of gentamicin, tobramycin, and amikacin in combination with β-lactam antibiotics, 22% of the aminoglycoside recipients had documented audiometric toxicity compared with 7% of cefotaxime-treated patients.[349] In a different study of 53 subjects administered gentamicin, tobramycin, or amikacin for at least 4 days, loss was unilateral in 55% and bilateral in 45% of the patients, and hearing loss was initially detected after a mean of 9 days of therapy.[379]

Aminoglycosides penetrate into endolymph and cochlear and vestibular tissue[380] cells either by endocytotic uptake or by mechano-electrical transduction channels[381] and lysosomal accumulation after transstrial trafficking.[382–384] In experimental animals, aminoglycosides can be detected in inner ear fluid within 3 hours of administration, but cochlear damage requires 3 weeks of daily injections.[376,385,386] The precise mechanism of cochlear toxicity has eluded detection.[387–389] As in renal tubular cells, there is evidence for aminoglycoside-induced apoptotic cell death in cells of both the organ of Corti and the vestibular apparatus.[390] Hair cell loss has been considered irreversible. However, animal studies in nonmammals and mammals have documented potential regeneration.[391–393]

The greatest risk for cochlear toxicity may be genetic predisposition.[394] In numerous reports, deafness has developed in family members of multiple pedigrees after treatment with an aminoglycoside and has been associated with five or more different mutations in the mitochondrial 12S rRNA gene,[395–404] which may result in greater binding affinity. No genetic predisposition to aminoglycoside vestibular or renal toxicity has been identified.

Human toxicity is related to the dose and duration of aminoglycoside therapy.[376] Ototoxicity is related to the AUC of concentrations in cochlear endolymph, itself correlated with AUC in serum.[405] Thus the same total daily dose will result in the same incidence of ototoxicity, independent of the frequency of dosing.[186,187,189,372] Measurable differences in the risk of cochlear toxicity between gentamicin, tobramycin, amikacin, and netilmicin are minimal and less than some chemotherapeutic agents.[379,406–416] Prolonged therapy beyond 10 days, renal or hepatic impairment, and prior exposure to aminoglycosides are major risk factors.[413–415,417–419]

Concomitant loop diuretics, vancomycin, and loud ambient noise increase the risk of cochlear toxicity.[376,410–412] The use of aspirin reduced the incidence of ototoxicity from 13% to 3%.[406,420]

Vestibular Toxicity

The target of drug-related vestibular toxicity is the type I hair cell of the summit of the ampullary cristae.[421] The true incidence of vestibular toxicity in ill patients is virtually impossible to determine. Because vestibular injury is bilateral and initially symmetrical, it can be compensated by visual and proprioceptive cues, so patients can sustain considerable injury before the appearance of symptoms or clinical findings. Suspicion is raised at the bedside by complaints of nausea, vomiting, and imbalance.[377,422] Visual blurring with head movement (i.e., oscillopsia) may occur. Symptoms are exacerbated in the dark, when the eyes are closed, with moving or uneven surfaces, and in other situations that block compensatory pathways. Nystagmus may be evident. Systematic surveillance of patients with electronystagmography is seldom performed; in one clinical study using electronystagmographic surveillance, abnormalities were demonstrated in 4% to 6% of patients receiving gentamicin or amikacin.[351,352] There are no data that compare, in a controlled fashion, the toxic potential of the commonly prescribed aminoglycosides.

Vestibular injury can be unilateral or bilateral and mild or severe.[377,422] Functional recovery, even with bilateral damage, was reported to occur in up to 53% of patients at 10 days to 9 months after cessation of drug exposure.[422–425] In addition to visual and proprioceptive compensation, recovery may be due to hair cell regeneration, as demonstrated in animal models.[406,426,427] The relevance of the latter to humans is unclear.

Vestibular hair cells are purposely damaged by gentamicin as therapy for Meniere disease that fails to respond to conservative measures.[428,429] Injection into the middle ear allows gentamicin to pass through the round window membrane, penetrate the labyrinth, and destroy hair cells. A single injection is reported to effect good control of vertigo in 75% of patients, with minimal sensorineural hearing loss.[430]

Neuromuscular Blockade

Neuromuscular blockade after aminoglycoside administration is a rare but serious and potentially lethal adverse effect. Neuromuscular blockade has been described in patients administered neomycin, streptomycin, kanamycin, tobramycin, gentamicin, amikacin, or netilmicin.[213,431] In general, blockade has occurred in clinical situations in which a disease state or a concomitant drug interferes with neuromuscular transmission.[431–437] Drug exposure may have been a result of intraperitoneal, intravenous, intramuscular, intrapleural, oral, topical, or retroperitoneal administration.[213,431] Aminoglycoside therapy in ventilated patients or others in intensive care has not generally been associated with adverse effects.[207,438,439] Blockade

[d]References 308, 309, 345, 346, 350, 368–371.

results from inhibition of the presynaptic release of acetylcholine as well as blockage of postsynaptic receptor sites of acetylcholine.[440–443]

CLINICAL INDICATIONS

The aminoglycosides are effective in empirical treatment of infections caused by or suspected to be caused by aerobic gram-negative bacilli including *P. aeruginosa*. Aminoglycosides have in vitro activity against *S. aureus,* but resistant small colony variants may appear within 24 hours unless a concomitant antistaphylococcal β-lactam or vancomycin is administered.[444] Activity against *Enterococcus* spp. requires a concomitant active penicillin or vancomycin. Aminoglycosides have no practical activity against pneumococci or anaerobic organisms. For reasons of anticipated spectrum of activity or to achieve an additive or synergistic effect, aminoglycosides are often combined with a β-lactam antibiotic, vancomycin, or a drug active against anaerobic bacteria.

The efficacy of empirical aminoglycoside therapy has been documented in published symposia describing the results of clinical trials that served as the basis for licensure and subsequent trials that compared one aminoglycoside with another or with a β-lactam.[e] In febrile neutropenic patients, a high failure rate was experienced after monotherapy with an aminoglycoside; therefore in such patients the aminoglycosides are administered in combination with a β-lactam antibiotic active against aerobic gram-negative bacilli.[367] Guidelines on the treatment of the febrile neutropenic patient suggest avoidance of aminoglycosides, if possible; instead, empirical monotherapy with a carbapenem or broad-spectrum β-lactam is used.[445]

Given that optimal peak/MIC and AUC/MIC pharmacodynamic ratios are obtained only for organisms with MICs of 0.5 μg/mL or less with conventional doses of gentamicin, netilmicin, and tobramycin (2 μg for amikacin) and MICs of 1.0 μg/mL with doses of 7 mg/kg,[9] it is not surprising that several reviews have demonstrated inferior clinical efficacy of aminoglycoside monotherapy in severe gram-negative infections compared with therapy with β-lactams and fluoroquinolones.[367,459] A review emphasized individualized dosing based on pharmacodynamics to optimize care of critically ill patients.[460] Although aminoglycosides have been used in combination with β-lactams and fluoroquinolones to enhance killing and improve clinical efficacy, most studies have failed to demonstrate better outcomes with combinations compared with monotherapy.[461]

Bacteremia

In contrast to most older studies[5,462] and a more recent retrospective review of *P. aeruginosa* bacteremia,[124] other more recent studies demonstrate improved outcome in patients with septic shock and gram-negative bacillary bacteremia treated with a combination of aminoglycoside plus β-lactam including carbapenem-resistant pathogens.[6,12,463] Combination therapy provided a greater degree of initial appropriate therapy than β-lactam monotherapy, broader coverage than fluoroquinolones, and improved outcomes even in neutropenic patients.[464,465] Reduced endotoxin release seen with aminoglycoside therapy[355,356] may contribute to the diminished early mortality observed with combination therapy in patients with septic shock. Combination therapy in selected cases is endorsed in the most recent international guidelines for management of severe sepsis.[466] Short-course therapy was not associated with increased nephrotoxicity.[466]

A detailed analysis and a meta-analysis of use of aminoglycosides in the treatment of bacterial endocarditis have been published.[205,206,467,468] The use of aminoglycosides in combination with a β-lactam or vancomycin may be beneficial for patients with streptococcal or enterococcal endocarditis. The standard dosage to achieve a synergistic effect is 1 mg/kg intravenously every 8 hours; newer regimens have used 12- and 24-hour intervals.[469] The risk of nephrotoxicity increased in parallel with the duration of therapy.[358] For viridans streptococcal endocarditis, three times–daily, twice-daily, and once-daily regimens appear to be of equal efficacy in reported clinical trials.[205,206,447,467–470]

The long-held practice of administering combination β-lactams plus aminoglycosides for staphylococcal bacteremia and endocarditis has been challenged by some investigators,[471,472] who recommended against the addition of low-dose gentamicin (1 mg/kg every 8 hours) because of its added nephrotoxicity. Others have instead emphasized the suboptimal dosing strategy used[473] or emphasized the significant earlier (2 days vs. 4 days) defervescence.[474] Aminoglycoside combinations remain the standard of care for enterococcal bacteremia and endocarditis, although dual β-lactam regimens are being used as alternatives.[475,476]

Pneumonia

Aminoglycoside use in pneumonia is typically reserved for hospital-acquired or hospital-associated gram-negative bacillary respiratory tract infections, including infections seen in patients on ventilators or with CF. Combination therapy with a β-lactam yields superior results[477] compared with aminoglycosides alone, without generally improving outcome over β-lactam monotherapy for Enterobacteriaceae.[478] The role of combination therapy for *P. aeruginosa* pneumonia is still unclear, with one meta-analysis suggesting significant mortality benefit,[478] but another large study showing no additional benefit as long as the isolate was susceptible to more than one agent.[124]

Aerosolized aminoglycosides, initially used to treat CF exacerbations,[217–222] have shown promise in chronic bronchiectatic infections[479,480] and ventilator-associated pneumonias. Most of the infections studied have involved *P. aeruginosa* and the inhaled aminoglycoside used in conjunction with a systemic β-lactam. Aerosolized aminoglycosides were associated with improved clinical and microbiologic cure rates, with less nephrotoxicity.[481–483]

Intraabdominal Infections

Current guidelines on empirical therapy for intraabdominal infections of moderate or high severity do not recommend the combination of an aminoglycoside with metronidazole.[449] This judgment is based on both the toxic potential of the aminoglycosides and the availability of equally efficacious regimens. Two meta-analyses of more than 5000 patients (including more than 3000 enrolled in randomized controlled trials) demonstrated clinical inferiority of aminoglycoside therapy (usually as clindamycin-gentamicin combination) to its comparator, β-lactam, for intraabdominal infections. Nephrotoxicity was seen more often with aminoglycoside therapy, but overall toxicity was equivalent, as were all-cause mortality and mortality attributable to infection.[484] Alternative first-choice regimens include a β-lactam–β-lactamase inhibitor combination (e.g., piperacillin-tazobactam) plus a fluoroquinolone or monotherapy with a carbapenem.

Urinary Tract Infections

A systemic review and meta-analysis of randomized controlled trials in nearly 2500 patients enrolled in 26 trials showed that aminoglycoside monotherapy was equally effective as comparators in terms of all-cause mortality and treatment failure.[446] Few trials enrolled patients with sepsis. A higher rate of bacteriologic failure and nephrotoxicity was observed with aminoglycosides. The duration of therapy was not recorded in the report, so it is unclear if 5 to 7 days of therapy would provide equivalent clinical efficacy to longer courses, given the presence of therapeutic aminoglycoside levels for most pathogens in urine for 72 hours or longer after a single dose. Intravesicular gentamicin has been investigated, with anecdotal success, for recurrent urinary tract infections in intermittently catheterized patients.[485]

Cystic Fibrosis

Patients with CF demonstrate altered aminoglycoside pharmacokinetics requiring much larger doses of drug to achieve therapeutic serum levels.[486,487] The frequency of nephrotoxicity in patients with CF is less than that in patients without CF.[488,489] The prevalence of hearing loss after aminoglycoside therapy in adult patients (18–37 years of age) with CF is 17%, which is roughly the same as the rate in patients without CF. However, the risk per course of treatment is 2% in patients with CF compared with 7.5% in patients without CF.[490] It is unclear how CF might protect against aminoglycoside cochlear toxicity.

The Cochrane Database of Systematic Reviews provides updated, periodic critical evaluation of the use of aminoglycosides and other antiinfectives in the treatment of pneumonia in patients with CF. Examples include single versus combination intravenous antibiotic

[e]References 4, 5, 347, 374, 375, 445–458.

therapy, nebulized antipseudomonal antibiotics, once-daily aminoglycoside therapy, and elective versus symptomatic antibiotic therapy.[221,491–495]

In 10 placebo-controlled trials of nebulized antipseudomonal antibiotics that included 758 patients,[221] patients receiving treatment had a 12% increase in forced expiratory volume in 1 second and a reduced odds ratio (0.69; 95% confidence interval, 0.5–0.96) of need for hospitalization. Over time, the incidence of aminoglycoside-resistant *P. aeruginosa* was greater in the treatment group, although one study demonstrated safety and tolerability after 8 weeks.[223]

Within 2 hours after the dose, sputum concentrations fall to approximately 14% of the levels found at 10 minutes after inhalation.[220] Absorption into serum is low. The average serum drug concentration 1 hour after inhalation was 1.0 μg/mL (range, 0.2–3.0 μg/mL).[222] Ototoxicity has not been reported, but transient tinnitus occurred in a few individuals during clinical trials. Nephrotoxicity has not been observed. Aerosol therapy presents advantages of higher local and less systemic exposure, self-administration at home, and improvement in lung function with a reduced burden of *P. aeruginosa*.

PROPHYLAXIS

Clinical practice guidelines for antimicrobial prophylaxis in surgery[496] suggest gentamicin or tobramycin, 5 mg/kg given intravenously, as an alternative in patients with β-lactam allergy in genitourinary and gastrointestinal procedures. For patients with valvular heart disease, prophylaxis is no longer recommended solely to prevent endocarditis. For patients with a known or possible enterococcal urinary tract infection, it is reasonable to include drugs with antienterococcal activity in the perioperative regimen for gastrointestinal or genitourinary procedures.[497]

The risk of infection after elective colorectal procedures was significantly reduced by mechanical cleansing of the bowel plus oral administration of, usually, neomycin and erythromycin or metronidazole in addition to standard intravenous antibiotic prophylaxis in controlled trials.[496,498] A controlled trial demonstrated that an oral selective digestive decontamination containing gentamicin effectively eradicated carbapenem-resistant *Klebsiella pneumoniae* gastrointestinal carriage[499] and may be used in nosocomial outbreaks.[500] However, the safety and efficacy of topical gentamicin in cardiac surgery have not been clearly established.[496,501] Multiple tunneled-catheter antibiotic-lock studies including a prospective randomized trial[502] have demonstrated reduced catheter-related infections, but emergence of resistant pathogens remains a concern.[503]

Spectinomycin and Gonorrhea

Spectinomycin has been not available in the United States since 2006 but may be available in other countries. It was previously recommended for pregnant women, patients in areas with a high prevalence of fluoroquinolone resistance, and men who have sex with men. It showed 98% efficacy in uncomplicated urogenital and anogenital gonococcal infections but only 52% efficacy in gonococcal infections involving the pharynx, where it does not reach therapeutic concentrations.[452] It is not effective in the treatment of infections with *Treponema pallidum* or *Chlamydia trachomatis*. The drug is neither nephrotoxic nor ototoxic. It is an alternative therapy for patients who are allergic to β-lactams and for patients who are infected with resistant strains of gonococci. No intravenous form of the drug is available. Alternatively, gentamicin has been used to treat urogenital gonococcal infection.[504]

Aminoglycosides in Orthopedic Surgery

Antibiotic-impregnated cement is used with increasing frequency in primary hip and knee arthroplasties as well as revision procedures of infected total joint arthroplasties,[496] for which the FDA has approved premixed aminoglycoside in bone cement products. Incorporation of larger amounts of antibiotic, usually gentamicin or tobramycin, allows release of higher drug concentrations but may adversely affect mechanical properties. Concentrations and properties vary among producers.[505–510] Persistence of bacterial growth as adherent biofilms remains a potential problem,[444,509,511] and nephrotoxicity has been reported.[512] To date, prophylactic use in primary joint arthroplasty appears to be favorable, but a multicenter evaluation failed to show reduction in the risk of infection,[513] with an increased risk of nephrotoxicity.[514] A review of 20 mostly uncontrolled reports of antibiotic-containing spacers did not allow evaluation of whether such adjunctive therapy provided additional benefits to systemic antibiotic therapy.[515] Prospective trials in aminoglycoside-containing beads for established osteomyelitis and prosthetic joint–associated infections are needed.[516]

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The complete reference list is available online at Expert Consult.

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26 Tetracyclines, Glycylcyclines, and Chloramphenicol

Matthew Moffa and Itzhak Brook

SHORT VIEW SUMMARY

DOXYCYCLINE
- The usual adult dose is 100 mg PO or IV every 12 hours.
- For patients with renal or hepatic failure, no dose adjustment is required.
- Cerebrospinal fluid (CSF) penetration is low.
- Common adverse effects include gastrointestinal upset, photosensitivity, rash, *Candida* vaginitis, and dental staining in children.
- Doxycycline is contraindicated in children and in pregnant or breastfeeding patients.
- There are no important drug-drug interactions.
- Indications are as follows:
  - Used to treat rickettsioses, scrub typhus, ehrlichiosis, anaplasmosis, psittacosis, actinomycosis, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* Lyme, syphilis, rat bite fever, *Chlamydia trachomatis* (including cervicitis, urethritis, lymphogranuloma venereum, and trachoma), Whipple disease, community-associated methicillin-resistant *Staphylococcus aureus*
  - Used in combination for brucellosis, tularemia, malaria, *Helicobacter pylori,* some rapid-growing mycobacteria, some filaria *(Wolbachia), Vibrio vulnificus*
  - Used for prophylaxis against leptospirosis, malaria, infections caused by tick bite (Lyme), and bioterrorism agents
  - Exposure to anthrax, tularemia, plague, Q fever, or brucellosis

TETRACYCLINE
- The usual adult dose is 250 to 500 mg PO every 6 hours.
- In patients with renal failure, reduce the dose.
- Contraindications, adverse effects, and indications are the same as for doxycycline.

MINOCYCLINE
- The usual adult dose is 200 mg PO or IV, then 100 mg every 12 hours.
- In patients with renal or hepatic failure, no dose adjustment is necessary.
- CSF penetration is low.
- Common adverse effects are similar to those with doxycycline, but with more vertigo.
- With regard to indications, doxycycline usually preferred, although minocycline is preferred for nocardiosis.

TIGECYCLINE (A GLYCYLCYCLINE)
- The usual adult dose is a loading dose of 100 mg, then 50 mg IV every 12 hours.
- In patients with renal failure, no dose adjustment is required.
- In patients with severe hepatic failure (Child-Pugh C), the dose is 100 mg loading, then 25 mg every 12 hours.
- CSF penetration is low.
- Common adverse effects are similar to those with doxycycline, except that nausea and vomiting are more frequent. Other effects include anorexia, dry mouth, and dysgeusia. There is a small increase in mortality across all clinical trials; the US Food and Drug Administration (FDA) has issued a boxed warning.
- Indications include complicated skin and skin structure infections, complicated intraabdominal infections, community-acquired bacterial pneumonia, and off-label use in combination with other drugs for infections with susceptible multidrug-resistant, gram-negative bacilli.

CHLORAMPHENICOL
- The usual adult dose is 50 mg/kg/day, divided into 6-hour doses. Chloramphenicol is available only in intravenous formulation in the United States.
- In patients with renal failure, no dose adjustment is required. Decrease dose or avoid in patients with hepatic failure.
- CSF penetration is moderate.
- Adverse effects include neutropenia, aplastic anemia, optic neuritis, gray baby syndrome (circulatory collapse in infants), and rash.
- There are no indications for use; this agent has been replaced by safer drugs.

TETRACYCLINES

Historical Overview and Classification

Tetracyclines have been an important class of broad-spectrum antibiotics since the discovery of chlortetracycline in 1948 by mycologist Benjamin M. Duggar.[1] They are bacteriostatic with a wide range of activity, including gram-positive bacteria, gram-negative bacteria, intracellular organisms, and protozoan parasites. Duggar derived chlortetracycline from *Streptomyces aureofaciens,* a golden-yellow bacterium found in soil. In 1950, oxytetracycline was isolated from *Streptomyces rimosus.* Tetracycline was later prepared by the catalytic dehalogenation of chlortetracycline in 1953 at Lederle Laboratories, and was independently derived from oxytetracycline at Pfizer Laboratories during that same time period.[2,3] Doxycycline is a semisynthetic derivative of oxytetracycline and became available in 1967. Minocycline, also derived semisynthetically, was derived in 1972.

Shortly after the discovery of tetracyclines, resistance developed, in large part because of their extensive clinical and nonclinical uses, including as growth promoters in animal feeds.[4,5] This widespread use has selected for a large number of resistant determinants collectively termed the *tetracycline resistome.*[6] This resistance led to a period of time when tetracyclines were replaced by newer antibiotics, such as the fluoroquinolones in the 1970s and 1980s. Like every other antibiotic, the fluoroquinolones would also fall to the selective pressure of antimicrobial resistance, leading to the development of newer, semisynthetic tetracyclines called *glycylcyclines.* In 2005, tigecycline became the first glycylcycline approved by the US Food and Drug Administration (FDA) for treatment of complicated skin and soft tissue infections and complicated intraabdominal infections (cIAIs). Later, in 2009, it was approved for use in community-acquired pneumonia (CAP).

Tetracyclines as a class are commonly divided according to two distinct classification methods: duration of action or year of discovery (Table 26.1, Fig. 26.1). Short-acting tetracyclines include the first-generation oxytetracycline and tetracycline. Intermediate-acting tetracyclines include another first-generation member, demeclocycline. Of note, demeclocycline is rarely used for infections. Its main side effect is nephrogenic diabetes insipidus. Thus it has found its niche in treatment of hyponatremia in the setting of the syndrome of inappropriate antidiuretic hormone secretion, first reported in the 1970s.[7] Long-acting tetracyclines include the second-generation agents doxycycline and minocycline and the third-generation glycylcycline tigecycline.

Structure and Mechanism of Action

Tetracyclines all share a four-benzene ring as their core structure, with a hydronaphthacene nucleus (see Fig. 26.1). Variations in gastrointestinal

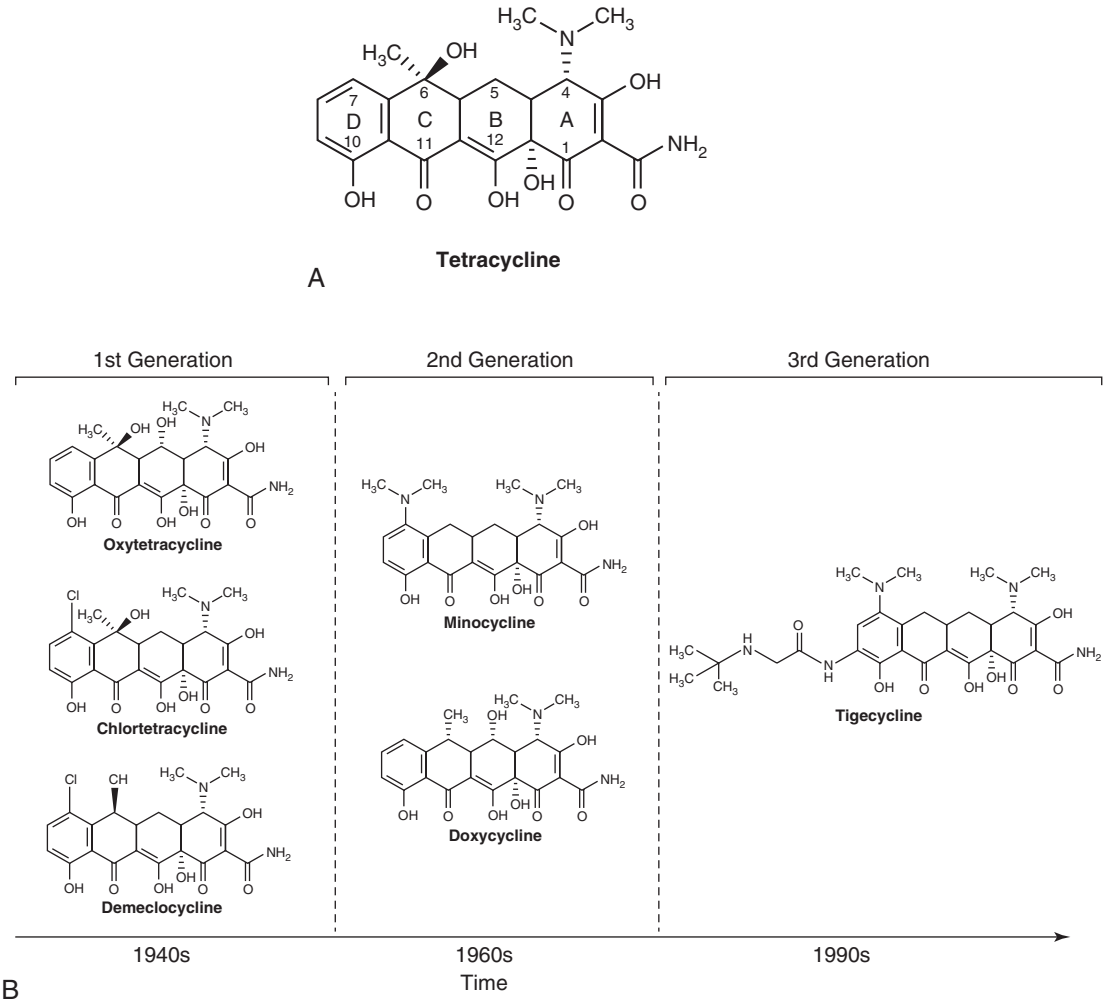

FIG. 26.1 Chemical structures of various tetracycline antibiotics. (A) Structure of tetracycline. (B) Advances in new-generation tetracycline development over a period of time. *(From Thaker M, Spanogiannopoulos P, Wright GD. The tetracycline resistome.* Cell Mol Life Sci. *2010;67:419–431.)*

TABLE 26.1 Tetracycline Formulations Currently Available in the United States

GENERIC NAME	MAJOR BRAND NAME (COMPANY)	PREPARATION	USUAL ADULT ORAL DOSE	NOTES
Short-Acting				
Oxytetracycline	Terramycin (Pfizer)	Capsules: 125, 250 mg Syrup: 125 mg/5 mL	500 mg q6h	No longer widely used
Tetracycline HCl	—	Capsules: 250, 500 mg Syrup: 125 mg/5 mL	500 mg q6h	
Intermediate-Acting				
Demeclocycline HCl	Declomycin (Wyeth)	Tablets: 150, 300 mg	150 mg q6h or 300 mg q12h	Used for syndrome of inappropriate antidiuretic hormone secretion
Long-Acting[b]				
Doxycycline	Vibramycin (Pfizer)	Capsules (hyclate): 50, 100 mg Tablets: 50, 100 mg Syrup (calcium): 50 mg/5 mL Syrup (monohydrate): 25 mg/5 mL	100 mg q12h	
Minocycline	Minocin (Wyeth) Solodyn ER tablets (Medicis)	Capsules and tablets: 50, 100 mg Suspension: 50 mg/5 mL Extended-release tablets 45, 90, 135 mg	200 mg, then 100 mg q12h 1 mg/kg/day	
Long-Acting, Third-Generation				
Tigecycline	Tygacil (Wyeth)	Vial: 50 mg lyophilized (reconstituted to 10 mg/mL)	100 mg, then 50 mg q12h	IV

[a]Other brands are available for some of the analogues.
[b]Long-acting agents exist in intravenous preparations and can be given at the same doses recommended for oral therapy (doxycycline 100-mg vial, 200-mg vial; minocycline, 100-mg vial).

absorption, affinity for multivalent cations, protein binding, and antimicrobial activity can be achieved with substitutions at carbons 5, 6, and 7 of the four-ring, six-membered carbocyclic structure, leading to variations in pharmacokinetic properties.[3]

Tetracyclines work by inhibiting bacterial protein synthesis. This is accomplished primarily by reversibly binding to the 30S ribosomal subunit of the bacteria. This inhibits the enzyme binding of aminoacyl-tRNA to the adjacent ribosomal acceptor site, which in turn prevents peptide chain elongation and inhibits protein synthesis.[2] Because the binding of tetracyclines to the 30S ribosomal subunit is reversible, it is postulated that this is the explanation as to why they exhibit bacteriostatic properties. For tetracyclines to get to the 30S ribosomal subunit, they need to be able to penetrate cell walls, which is accomplished through passive diffusion. With gram-negative organisms, tetracyclines become positively charged cation complexes, presumably with magnesium. They then use OmpF and OmpC porin channels to cross the outer membrane. After entering the periplasmic space, tetracycline dissociates, resulting in an accumulation of uncharged tetracycline. With gram-positive organisms, tetracyclines penetrate through the inner cytoplasmic membrane via an active transport system that depends on the ΔpH.[3,8] Tetracyclines also reduce bacterial pathogenicity by suppressing adhesion of bacteria to human cells. This is likely achieved through inhibition of the synthesis of a specific protein in the bacterial cell surface.[9]

Doxycycline displays additional protein synthesis inhibition in mitochondria through binding of the 70S ribosomes.[10] This enables it to exhibit activity against various protozoa because they contain mitochondria. Doxycycline also targets parasites via the apicoplast ribosomal subunits in *Plasmodium falciparum*. This occurs late in the malarial cell cycle, resulting in the slow antimalarial effect of doxycycline.[10,11]

Pharmacology

Administration and Dosing

Tetracycline

Tetracycline HCl comes in 250-mg and 500-mg capsules and in 125 mg/5 mL syrup. The usual adult oral dose is 250 mg every 6 hours or 500 mg every 6 hours for more serious infections. Larger doses do not provide additional benefit, and the excess drug is excreted in feces. Intravenous preparations of tetracycline are no longer used owing to their potential hepatotoxicity. Acute fatty liver has occurred with large intravenous doses, particularly during pregnancy. Tetracycline is labeled category D and is to be avoided in pregnancy. It should also be avoided in children, particularly those younger than 8 years during the period of tooth development in order to avoid permanent discoloration. Children are also at risk for retardation of bone development.

With renal impairment, tetracycline should be avoided because it can cause further deterioration of kidney function and the drug tends to accumulate in the serum.[12] Tetracycline is slowly removed by hemodialysis, but not very well by peritoneal dialysis.[13] Caution is advised in administering tetracycline in patients with hepatic impairment because this may result in liver damage.

Doxycycline

Doxycycline comes in various dose forms, but most typically in both 50-mg and 100-mg capsules and tablets. It is also available as 25 mg/5 mL and 50 mg/5 mL syrup. The usual adult dose is 100 mg every 12 hours and should be taken with at least 100 mL of water. For malaria chemoprophylaxis, the adult dose is 100 mg daily. Occasionally an intravenous preparation of doxycycline is required for certain cases of rickettsial infections, ehrlichiosis, or severe psittacosis. The usual adult dose is 200 mg followed by 100 mg every 12 hours. The dose should be given over 30 to 60 minutes and should be dissolved in 500 to 1000 mL of glucose or saline.[10] Like tetracycline, doxycycline is also pregnancy category D and should be avoided in children. If the benefits of doxycycline outweigh the risks in children, the pediatric dose is 2.2 mg/kg every 12 hours.

Unlike tetracycline, doxycycline is safe to use with renal impairment. Urinary excretion is reduced in renal impairment, but doxycycline does not accumulate in the serum because its gastrointestinal excretion increases.[14] During hemodialysis, only about 10% of the drug is removed.[15] With hepatic impairment, there are few pharmacokinetic data. Unlike tetracycline and minocycline, doxycycline does not appear to cause hepatitis.[16]

Minocycline

Like tetracycline and doxycycline, minocycline is primarily administered orally. It comes in 50-mg, 75-mg, and 100-mg capsules and tablets, and a 50 mg/5 mL suspension. There are also 45-mg, 90-mg, and 135-mg extended-release tablets. The usual adult dose is 200 mg followed by 100 mg every 12 hours. The dose is the same if minocycline is given intravenously. Each dose should be given over 30 to 60 minutes and must be dissolved in 500 to 1000 mL of glucose or saline.[17] Like tetracycline and doxycycline, minocycline is pregnancy category D and should also be avoided in children. If minocycline needs to be given to children, the pediatric dose is 4 mg/kg followed by 2 mg/kg every 12 hours.

With impaired renal function, various studies have shown contrasting results. Minocycline does not accumulate in the serum in patients with renal failure, and excretion in such patients is not significantly reduced.[18,19] This is because only a small amount of drug is eliminated in the urine. Other reports have found that minocycline can exacerbate preexisting renal insufficiency and can possess a prolonged serum half-life, which is directly related to the severity of any renal insufficiency.[20,21] With hemodialysis and peritoneal dialysis, minocycline pharmacokinetics are not significantly altered.[18,22] In cirrhotic patients, no changes for minocycline are observed.[22]

Absorption and Bioavailability

The absorption of the tetracyclines occurs primarily in the stomach and proximal small bowel. Tetracycline has a bioavailability of 77% to 88%, and maximum serum concentrations are reached 2 to 4 hours after standard doses with a serum half-life of 7 hours.[2,23] Doxycycline is almost completely absorbed in the duodenum and has a prolonged serum half-life of 12 to 16 hours, with peak serum levels usually achieved 2 to 3 hours after administration.[10] Minocycline is almost completely absorbed in the stomach, duodenum, and jejunum. It peaks in serum after 2 hours and also has a prolonged half-life of 16 hours after the first dose, and up to 21 hours after repeated doses.[17,20,24]

Doxycycline and minocycline absorption are not significantly altered by the administration of food, with levels decreased by less than 20%.[25,26] In contrast, tetracycline absorption decreases by approximately 50% when administered with food.[26] Multivalent cations (such as aluminum, calcium, iron, and magnesium) chelate with the tetracyclines, resulting in a decrease in drug absorption by 50% to 90%. An interval of 3 hours between the ingestion of tetracyclines and cations prevents this interaction.[27]

Drug Distribution

The tetracyclines penetrate well into various body fluids and tissues. Protein binding varies among drugs. Doxycycline is the highest protein-bound drug, estimated between 82% and 93%, followed by minocycline at 70% to 80% and tetracycline at 24% to 65%.[3,13,17,28] Tissue and fluid penetration differs on the basis of how lipid soluble each compound is. Doxycycline has been reported to be 5 times as lipophilic as tetracycline, and minocycline is 10 times more lipophilic than tetracycline.[29,30]

Serum concentrations of tetracycline rise slowly after oral administration, and C_{max}, depending on the dose, is generally in the range of 1 to 5 μg/mL.[28] Tetracycline penetrates readily into pleural, ascitic, and synovial fluids and placental-cord serum.[2] In maxillary sinus secretions, tetracycline concentrations can nearly equal serum concentrations with repeated administration.[31] However, tetracycline can be detected in only low concentrations in saliva and tears. Sputum levels of tetracycline in the range of 0.4 to 2.6 μg/mL have been detected after oral administration of 250 mg every 8 hours.[32] Cerebrospinal fluid (CSF) levels of tetracycline are about 10% of the simultaneous serum concentration.[2] Tetracycline penetrates readily into breast milk but chelates with milk, thus lowering its bioavailability.[33]

The serum C_{max} of doxycycline peaks at around 1.7 to 2 μg/mL after oral administration of 100 mg.[28] With oral administration of 200 mg,

this increases to 2.6 to 5.9 μg/mL. Doxycycline concentrates in the bile at 10 to 25 times greater levels than in the serum.[34] In thoracic duct lymph and peritoneal fluid, doxycycline concentrations are about 75% of serum levels.[35] In the prostate, doxycycline concentrations are up to 60% of serum levels.[36] After an intravenous dose of 200 mg was given to patients with pleurisy, pleural fluid levels of doxycycline were 25% of serum levels after 2 hours.[37] Blister fluid model studies have shown that interstitial fluid concentrations of doxycycline are 54% of serum levels.[38] Lower levels of doxycycline have been noted in sputum (8%–25%), and in bone (2%–6% orthopedic, 86% mandible), skin, subcutaneous fat, and tendon tissue.[39–42] In the CSF, doxycycline penetration has been studied in both neuroborreliosis and neurosyphilis. In patients with Lyme borreliosis treated with doxycycline 200 mg orally every 12 hours, CSF penetration was noted to be 15% with a concentration of 1.1 μg/mL. At a dose of 100 mg orally every 12 hours, the CSF concentration was only 0.6 μg/mL, suggesting that treatment should be with the higher dose.[43] In five patients with latent syphilis or neurosyphilis receiving 200 mg orally every 12 hours, doxycycline CSF penetration was 26% with a concentration of 1.3 μg/mL, suggesting doxycycline as an alternative to penicillin.[44] Like tetracycline, doxycycline penetrates readily into breast milk, with levels of up to 40% of plasma levels.[33] Because it is less bound to calcium than the other tetracyclines, an infant being breastfed is at greater risk of side effects.

After a single 200-mg dose, minocycline achieves a C_{max} of 3 to 3.6 μg/mL.[28] Because minocycline is the most lipophilic of the tetracyclines, it penetrates the most readily into tissues and bacterial cells.[45] The highest concentrations are found in the thyroid, lung, gastrointestinal tract, liver, gallbladder, and bile. Other tissues with concentrations higher then serum levels are the prostate, uterus, ovaries, fallopian tubes, breast, skin, tonsils, maxillary sinuses, and eyes.[17,22,30,46,47] Minocycline penetrates into CSF better than the other tetracyclines but is able to achieve only low levels.[18,22,30] Minocycline can gain higher concentrations in saliva than other tetracyclines, likely explaining why it is effective at eliminating meningococcal carriage.[48] As with tetracycline, bioavailability in breast milk is low because of chelation with milk.[33]

Drug Elimination

The tetracyclines are each eliminated slightly differently. Tetracycline is eliminated primarily in the kidneys, and about 30% to 60% of an oral dose is excreted in the urine.[2,3] The drug accumulates with renal insufficiency, which is why it should be avoided in such patients. About 20% to 60% is eliminated in feces.[2] With doxycycline, usually less than 30% of an oral dose is renally excreted.[3,49,50] However, unlike tetracycline, fecal excretion is increased in the setting of renal impairment and prevents accumulations of the drug. As much as 90% of doxycycline can be excreted in feces. Minocycline is extensively metabolized in the liver to produce at least six inactive metabolites. Only about 4% to 19% is eliminated by the kidneys, and 20% to 34% is excreted in the feces.[19,22,30,51]

Antimicrobial Activity

The tetracyclines as a class have a wide spectrum of antimicrobial activity. Similar susceptibility patterns are displayed among the nonglycylcycline members. They have activity against many aerobic and anaerobic gram-positive and gram-negative bacteria, in addition to intracellular organisms and protozoan parasites. Because they are bacteriostatic and many organisms have developed resistance over the years, they have been replaced by other antibiotics as first-line therapy in the majority of cases. When interpreting minimal inhibitory concentration (MIC) results, tetracycline is generally used as the class representative. However, there may be times when specific testing for minocycline or doxycycline is warranted because some organisms may still be susceptible even when resistant or with intermediate resistance to tetracycline.

Most bacterial organisms, including Enterobacteriaceae, non–lactose-fermenting gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., and anaerobes, are considered susceptible to tetracycline when the MIC is 4 μg/mL or less. At 8 μg/mL, tetracycline is considered intermediately active. Resistance is defined as 16 μg/mL or greater. *Haemophilus* spp., β-hemolytic streptococci, and viridans-group streptococci have lower MIC breakpoints, with susceptible, intermediate, and resistant set at 2 μg/mL or less, 4 μg/mL, and 8 μg/mL or more, respectively. Even lower is *Neisseria gonorrhoeae,* with susceptible, intermediate, and resistant set at 0.25 μg/mL, 0.5 to 1 μg/mL, and 2 μg/mL or more, respectively. *Streptococcus pneumoniae* has susceptible, intermediate, and resistant breakpoints of 1 μg/mL or less, 2 μg/mL, and 4 μg/mL or more for tetracycline, and 0.25 μg/mL or less, 0.5 μg/mL, and 1 μg/mL or more for doxycycline, respectively. The susceptibility breakpoint of minocycline for *Neisseria meningitidis* is 2 μg/mL or less.[52]

Gram-Positive Bacteria

Tetracyclines possess broad activity against gram-positive organisms, including community-acquired *Staphylococcus aureus* and *S. pneumoniae.* Data from the SENTRY Antimicrobial Surveillance Program from 1997 through 1999 evaluated the susceptibilities of 15,439 patients infected with *S. aureus* and 6350 infected with coagulase-negative staphylococci (CoNS).[53] Samples were taken from various parts of the globe. In the United States, 94.2% of methicillin-susceptible *S. aureus* (MSSA) strains and 83.7% of methicillin-resistant *S. aureus* (MRSA) strains were susceptible to tetracycline. Results were similar in isolates from Canada, whereas those obtained from Latin America, Europe, and the Western Pacific had much lower MRSA susceptibilities to tetracycline, 17.8% to 41.4%. In the United States, CoNS were susceptible to tetracycline in 82.9% of the oxacillin-sensitive strains and 79.6% of the oxacillin-resistant strains. These findings were similar to those in the other regions.[53] More recent studies have also shown that the majority (80%) of MRSA isolates were susceptible to doxycycline and minocycline.[54]

Reports of *S. pneumoniae* resistance to doxycycline range geographically from 2% to more than 20%, limiting the use of this drug for severe pneumococcal infections.[10,55–56,57] Resistance may be more than 60% in penicillin-resistant strains.[57] Data on β-hemolytic streptococci are lacking. Swedish studies have shown doxycycline resistance rates of 15% for *Streptococcus pyogenes* and 68% for group B streptococcal isolates.[58,59] Among *Enterococcus* spp., surveillance data from 1997 through 1999 observed resistance rates approaching 50% in North America, 60% in Europe, and 60% to 70% in the Asia-Pacific region.[60] *Actinomyces israelii* has shown susceptibility to tetracycline, and *Listeria monocytogenes* and *Bacillus anthracis* to both tetracycline and doxycycline.[61–64]

Gram-Negative Bacteria

As a class, tetracyclines also have a broad range of activity against gram-negative organisms, although they are infrequently used against Enterobacteriaceae. Doxycycline has shown good activity against *Yersinia pestis* and has more activity than tetracycline.[65,66] Among *Campylobacter jejuni* and *Campylobacter coli* strains, isolates that have resistance to ciprofloxacin tend to also be resistant to doxycycline.[67] Tetracyclines are useful in the treatment of *Vibrio* spp. in a wide range of clinical conditions from food-borne gastroenteritis to necrotizing skin and soft tissue infections.[68–70]

In a Spanish study with *Acinetobacter baumannii,* doxycycline had activity against only 30% to 40% of strains tested, whereas minocycline was active against 70% and tigecycline was active against 76%.[71] Doxycycline has excellent activity against *Burkholderia pseudomallei* with susceptibility rates above 96%, along with low rates of resistance developing during treatment.[72] *Stenotrophomonas maltophilia* is highly susceptible to doxycycline,[69,73] which also exhibits activity against *Aeromonas hydrophila*.[70,74] In a global collection of clinical isolates (*A. baumannii, S. maltophilia,* and *Burkholderia cepacia*), minocycline demonstrated the highest activity of the tetracyclines.[75] Anaerobes in the gastrointestinal tract, including the *Bacteroides fragilis* group, have shown susceptibility to doxycycline, but with higher MIC breakpoints.[76] *Brucella* spp. and *Bartonella* spp. are also highly susceptible to doxycycline, with low MIC values.[77,78]

Atypical Bacteria

Among the *Mycoplasma* spp., tetracyclines are highly active against *Mycoplasma pneumoniae*. *Mycoplasma hominis* is usually susceptible, whereas *Mycoplasma genitalium* is often doxycycline resistant.[79–81] *Legionella pneumophila* is susceptible to doxycycline in vitro, but this is dependent on the inoculum size because *Legionella* is intermediately susceptible to doxycycline with larger inocula.[82] *Chlamydia pneumoniae* and *Chlamydia psittaci* have also been shown to be susceptible to

doxycycline.[83,84,85] *Chlamydia trachomatis* is typically susceptible to the tetracyclines, although susceptibility testing is not standardized.[84,86]

Spirochetes and Rickettsiae

The tetracyclines play a prominent role in the treatment of spirochetes. Doxycycline is the mainstay treatment of Lyme disease caused by *Borrelia burgdorferi.*[87] In a recent study looking at doxycycline, tetracycline, and tigecycline activity against *B. burdorferi,* tigecycline had the lowest MIC_{90} (≤0.016 mg/L) versus 0.25 mg/L for both doxycycline and tetracycline.[88] For *Leptospira* spp., doxycycline has also been a mainstay of treatment.[89] Tetracycline has been shown to have activity against *Treponema pallidum.*[90] Among *Rickettsia* spp., tetracyclines display activity against the spotted fever group, scrub typhus, and epidemic typhus. Doxycycline has been shown to be the most active antimicrobial agent.[91,92] Doxycycline has also shown to be highly active against *Anaplasma phagocytophilum, Ehrlichia chaffeensis,* and *Ehrlichia canis.*[93]

Mycobacteria and Nocardia

Among mycobacteria, tetracyclines have activity among different species. Against the rapidly growing bacteria, doxycycline has been reported to have activity against 41% to 56% of *Mycobacterium fortuitum* strains. Less activity is seen against *Mycobacterium chelonae* (8%–26%) and *Mycobacterium abscessus* (4%–8%).[94–96] Similar results are seen with minocycline, although minocycline appears to be more active against *M. chelonae* and *M. fortuitum*. Minocycline also appears to have more activity against *Mycobacterium marinum* than doxycycline and has activity against *Mycobacterium kansasii* as opposed to doxycycline.[96–98] All of the tetracyclines show poor in vitro activity against *Mycobacterium avium* complex.[96] More recently, interest in using doxycycline against *Mycobacterium tuberculosis* has developed. A Russian study that evaluated second-line agents with activity against multidrug-resistant (MDR) *M. tuberculosis* found doxycycline to be active against 92.6% of the 68 isolates tested.[99] Doxycycline has also been shown to decrease matrix metalloproteinase activity in a cellular model and to suppress mycobacterial growth in vitro and in guinea pigs.[100]

Among the *Nocardia asteroides* complex, minocycline appears to have the greatest activity against these and a large number of *Nocardia farcinica* isolates.[10,101] Minocycline has also been shown to be more active than tigecycline, with an MIC_{90} of 2 μg/mL.[102]

Parasites

Tetracyclines are effective but slow-acting antimalarial drugs. They have been shown to specifically block expression of the apicoplast genome in cultured *P. falciparum,* resulting in the distribution of nonfunctional apicoplasts into daughter merozoites.[11] The tetracyclines have also been shown to have activity against *Toxoplasma gondii, Giardia lamblia, Trichomonas vaginalis, Leishmania major,* and *Entamoeba histolytica.*[17,103–105]

Clinical Uses

General

Tetracyclines previously were widely used for an array of respiratory, gastrointestinal, and genitourinary tract infections. The widespread increase in resistance along with the availability of newer, more bactericidal drugs has decreased the number of diseases for which these agents are considered to be the drugs of choice. For treatment of most diseases, tetracycline and doxycycline are interchangeable. Often doxycycline is the preferred agent because it can be given just twice a day, has fewer gastrointestinal side effects, and can be taken with food or milk. For a full table of therapeutic indications for tetracyclines, see Table 26.2.

Respiratory Tract Infections

According to the 2007 CAP practice guidelines of the Infectious Diseases Society of America, doxycycline was given a weak level III recommendation as empirical monotherapy in the outpatient setting in

TABLE 26.2 Therapeutic Indications for Tetracyclines

MAJOR INDICATIONS	SECOND-LINE TREATMENT	PROPHYLAXIS
Anaplasma (formerly *Ehrlichia*) *phagocytophilum* infection	*Acinetobacter baumannii* infections (sensitive strains)	Anthrax *(Bacillus anthracis)*
Anthrax inhalation, cutaneous postexposure	Acne	Colonic surgery
Bacillary angiomatosis in patients with human immunodeficiency virus infection (*Bartonella henselae* and *Bartonella quintana*)	*Actinomyces israelii* when penicillin is contraindicated	Lyme disease, after tick bite
Balantidium coli infection (infectious colitis)	Acute intestinal amebiasis (as adjunct therapy)	Malaria
Bartonellosis: Oroya fever and verruga peruana *(Bartonella bacilliformis)*	*Burkholderia mallei* (glanders) infections (only in combination with other drugs)	Plague *(Yersinia pestis)*
Brucellosis (plus rifampin, streptomycin, or gentamicin)	*Burkholderia pseudomallei* (melioidosis; only in combination with other drugs)	Traveler's diarrhea
Cat-scratch fever *(B. henselae)*	*Campylobacter fetus* infections	Treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx (minocycline)
Cervicitis due to *Chlamydia trachomatis*	*Clostridium* infections when penicillin is contraindicated	Tularemia *(Francisella tularensis)*
Cholera	*Dientamoeba fragilis*	
Community-acquired pneumonia	*Eikenella corrodens* infection	
Ehrlichia chaffeensis infection	Filariasis	
Granuloma inguinale *(Klebsiella granulomatis)*	Leptospirosis if penicillin contraindicated	
Inclusion conjunctivitis *(C. trachomatis)*	*Mycobacterium leprae* (only minocycline is active)	
Lyme disease *(Borrelia burgdorferi)*	*Nocardia* (minocycline)	
Lymphogranuloma venereum *(C. trachomatis)*	*Pasteurella multocida*	
Mycobacterial infections caused by *Mycobacterium marinum* and some isolates of *Mycobacterium fortuitum* and *Mycobacterium chelonae*	Rat-bite fever *(Spirillum minus, Streptobacillus moniliformis)*	
Nongonococcal urethritis	Syphilis, primary and secondary (patients with penicillin allergy; *Treponema pallidum*)	
Pelvic inflammatory disease	Vincent angina	
Peptic ulcer (with other agents; *Helicobacter pylori*)	Whipple disease *(Tropheryma whipplei)*	
Periodontitis	Yaws caused by *Treponema pertenue* when penicillin is contraindicated	
Pneumonia caused by *Chlamydia pneumoniae*		
Psittacosis and ornithosis *(Chlamydia psittaci)*		
Q fever *(Coxiella burnetii)*		
Relapsing fever, both louse- and tick-borne		
Rickettsial infections (spotted fever group and rickettsialpox)		
Scrub typhus *(Orientia tsutsugamushi)*		
Trachoma *(C. trachomatis)*		
Trench fever *(B. quintana)*		
Urethral infections caused by *C. trachomatis* or *Ureaplasma urealyticum*		
Vibrio vulnificus infection		

previously healthy patients with no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection.[106] It may also be used as an alternative to a macrolide in combination with a β-lactam antibiotic for use in outpatients with comorbidities or who are at risk for DRSP, and for those treated in inpatient non–intensive care unit settings.[106] Doxycycline has good coverage of the atypical pathogens encountered, such as *M. pneumoniae, L. pneumophila*, *C. pneumoniae,* and *C. psittaci.* Increasing rates of resistance with *S. pneumoniae* and *Haemophilus influenzae* limit doxycycline's use as monotherapy. Higher doses of doxycycline, 200 mg every 12 hours for 72 hours followed by standard 100 mg every 12 hours, have been used to treat moderate-to-severe legionellosis.[107,108] Tetracycline has been shown to be as effective as erythromycin for treatment of *M. pneumoniae.*[109] The drug of choice for psittacosis caused by *C. psittaci* has been shown to be doxycycline; intravenous therapy may be required.[110–112]

Gastrointestinal Tract Infections

Tetracycline has been extensively studied in the treatment of cholera, a *Vibrio cholerae* infection. Oral tetracycline has been shown to be effective in decreasing the amount and duration of diarrhea from cholera, and in eradicating the pathogen from stool.[113] It had been useful for prophylaxis of close contacts during an outbreak.[114] Later studies showed that a single dose of 1 g of tetracycline was effective in treating cholera.[115,116] Doxycycline has been shown to be as effective as tetracycline with a 4-day course of each drug, although bacterial elimination took slightly longer.[117] However, tetracycline resistance is now common throughout the world, and thus these drugs are no longer considered appropriate therapy unless susceptibility has been demonstrated.[118]

Second-line therapy for *Helicobacter pylori* infection typically includes a quadruple drug-based regimen with tetracycline 500 mg every 6 hours along with metronidazole, bismuth salt, and a proton pump inhibitor for 7 to 14 days. This combination has led to eradication rates close to 100%.[119] When comparing triple- versus quadruple-based regimens, a meta-analysis showed equal efficacy when used as first-line therapy, with similar compliance and side-effect profiles.[120] Doxycycline-containing regimens with amoxicillin, bismuth salt, and omeprazole for 1 week have been studied as salvage regimens with a reported 91% eradication rate.[121]

Doxycycline at a dose of 100 mg daily for 3 weeks has been shown to be effective in preventing traveler's diarrhea in regions with doxycycline-susceptible enterotoxigenic strains of *Escherichia coli* (ETEC).[122] Newer data suggest that the addition of doxycycline to ceftriaxone offers protection against the development of *Clostridioides difficile* (formerly *Clostridium difficile*) infection (CDI). In a study of 2305 patients, the incidence of CDI was 1.67 cases per 10,000 patient-days in those who received doxycycline along with ceftriaxone, compared with 8.11 per 10,000 patient-days in those who did not receive doxycycline along with ceftriaxone. For each day of doxycycline receipt, the rate of CDI was 27% lower than in patients who did not receive doxycycline.[123] This apparent protective effect of doxycycline was also observed in a large case-control study from 1999 to 2005 that evaluated multiple antibiotics.[124]

Genitourinary Tract Infections

Doxycycline is a mainstay of treatment for nongonococcal urethritis. Along with a single 1-g dose of azithromycin, doxycycline 100 mg orally twice daily for 7 days is recommended for treatment of uncomplicated *C. trachomatis* genital infection in the Centers for Disease Control and Prevention's 2015 sexually transmitted diseases treatment guidelines.[125] Cure rates with doxycycline have been reported to be 98% as compared with 97% for azithromycin, with similar tolerability noted.[126] A more recent study of a closed population receiving directly observed treatment for urogenital chlamydia infection found that the efficacy of azithromycin was 97%, and the efficacy of doxycycline was 100%. Azithromycin did not establish noninferiority.[127] Even when suboptimal compliance with doxycycline is documented, cure rates have been noted to remain high at 94%.[128] Other causes of nongonococcal urethritis, such as *Ureaplasma urealyticum* and *M. hominis,* are responsive to the tetracyclines but with less consistency. Resistant strains of *U. urealyticum* have been reported.[129] *M. genitalium* has been shown to be a persistent and recurring cause of urethritis in those treated with doxycycline.[130,131] Doxycycline is no longer recommended for the treatment of gonorrhea owing to increasing *N. gonorrhoeae* resistance.[132,133] In a randomized controlled pilot study, daily doxycycline taken prophylactically was associated with a decreased incidence of *N. gonorrhoeae, C. trachomatis,* or syphilis incident infections among a core group of high-risk human immunodeficiency virus (HIV)–infected men who have sex with men.[134]

The tetracyclines are active against the sexually transmitted infection lymphogranuloma venereum caused by *C. trachomatis* serovars L1, L2, and L3.[135] Clinical manifestations include inguinal lymphadenopathy and proctitis. Recommended therapy is doxycycline 100 mg orally twice daily for 21 days.[125] Granuloma inguinale (donovanosis) caused by *Klebsiella granulomatis* causes painless genital ulcerative disease and regional lymphadenopathy. It is rarely found in the United States and is endemic in certain parts of India, Papua New Guinea, central Australia, and southern Africa. Recommended therapy is doxycycline 100 mg orally twice daily for at least 3 weeks and until all lesions have completely healed.[125] Because of *Haemophilus ducreyi* resistance, doxycycline is not recommended for chancroid.[125]

In pelvic inflammatory disease (PID), a combination of initial intravenous cefotetan or cefoxitin with oral doxycycline 100 mg every 12 hours for 14 days is recommended. For outpatient treatment of mild-to-moderate PID, an intramuscular cephalosporin combined with 14 days of doxycycline with or without metronidazole is recommended.[125] When inpatient versus outpatient therapy in mild-to-moderate PID were compared, there were no differences in pregnancy rates or recurrence of PID.[136]

Spirochetal Infections

The tetracyclines are often used to treat illnesses caused by spirochetal infections. Doxycycline (100 mg orally twice daily for 10 to 21 days), along with amoxicillin or cefuroxime, is recommended for treatment of adult patients with early localized or early disseminated Lyme disease, caused by *B. burgdorferi,* associated with erythema migrans in the absence of specific neurologic manifestations or advanced atrioventricular heart block.[137] This is an A1 recommendation by the Infectious Diseases Society of America. In areas where human granulocytic anaplasmosis (HGA) is prevalent, doxycycline is preferred because it will treat both Lyme disease and HGA. Lyme arthritis should be treated with a longer course of 1 month.[138] Long-term doxycycline therapy has not been shown to have additional beneficial effects on health-related quality of life in patients with persistent symptoms attributed to Lyme disease.[139] A randomized controlled study has shown that a single 200-mg dose of doxycycline is effective in preventing clinical Lyme disease in patients with an *Ixodes scapularis* tick bite if given within 72 hours.[140] Although the recommended treatment of neuroborreliosis is parenteral agents, doxycycline 200 mg orally twice daily appears reasonable and an alternative for patients with a significant penicillin allergy.[141] A single oral 100-mg dose of doxycycline or a 500-mg dose of tetracycline is effective in treating louse-borne relapsing fever caused by *Borrelia recurrentis.*[142]

Doxycycline can also be used in patients with a significant penicillin allergy with treponemal infections. In primary or secondary syphilis caused by *T. pallidum,* doxycycline 200 mg orally once daily for 14 to 28 days may be appropriate.[143] A regimen of 100 mg orally twice daily for 14 days in early syphilis was shown to be just as effective as penicillin in treating early syphilis.[144] In HIV-infected individuals, doxycycline also appears to be effective in early syphilis, with similar serologic response to that in patients given penicillin.[145] In latent syphilis and neurosyphilis, five patients treated with doxycycline 200 mg orally twice daily for 21 days showed good CSF drug levels of doxycycline.[44] Small case reports of HIV-infected individuals with neurosyphilis treated successfully with oral doxycycline 200 mg twice daily for 28 days have been documented but would need further studying.[146] Minocycline was studied in three penicillin-allergic patients with neurosyphilis, at a dose of 100 mg twice daily for 14 consecutive days per month for 9 months. Clinical improvement was noted within 1 month and there were no significant side effects.[147] Nonvenereal treponemal infections, such as yaws (caused by *T. pallidum* subspecies *pertenue*), bejel or endemic syphilis (caused by *T. pallidum* subspecies *endemicum*), and pinta (caused

by *Treponema carateum*), can also be treated with tetracyclines as an alternative to penicillin.[148]

Doxycycline was shown to be as effective as penicillin or cefotaxime in treating severe leptospirosis in a randomized trial in northern Thailand. There was no difference in mortality or time to defervescence among the different treatment groups.[149] It has also been used as chemoprophylaxis against leptospirosis in endemic areas, with varying results. A systematic review found that the regular use of weekly 200 mg oral doxycycline increases the odds for nausea and vomiting with unclear benefit in reducing *Leptospira* seroconversion or clinical consequences of infection.[150]

Malaria Treatment and Chemoprophylaxis

Doxycycline is used for both treatment and chemoprophylaxis of malaria. Both *P. falciparum* and *Plasmodium vivax* are susceptible to doxycycline. Along with atovaquone-proguanil and artemisinin compounds, the combination of quinine and doxycycline (or tetracycline) is recommended for treatment of chloroquine-resistant *P. falciparum* strains.[151] Doxycycline is less often used to treat *P. vivax* infections owing to its slower rate of parasitic clearance and limited activity in the liver stages compared with other regimens.[152]

As for chemoprophylaxis, doxycycline has been shown to be as effective as mefloquine in regions with chloroquine-resistant *P. falciparum.* In two studies, doxycycline was protective in 99% to 100% of participants, although mefloquine was better tolerated in one study.[153,154] Other studies have shown that malaria developed in those taking doxycycline prophylaxis who ended therapy shortly after leaving an endemic area, likely a result of the fact that doxycycline has limited effect on preerythrocytic liver stages of malaria.[155–158] On the basis of these studies, it is recommended that doxycycline be taken for 4 weeks after returning from an endemic area.[159]

Other Infections

Doxycycline is the preferred agent for treating rickettsial infections such as Rocky Mountain spotted fever (RMSF), Mediterranean spotted fever, epidemic louse-borne typhus, murine typhus, scrub typhus, and tick typhus.[92,160–163] Regimens are usually between 5 and 15 days long.[92] However, shorter courses of doxycycline may also be appropriate. A randomized controlled trial of 43 patients with Mediterranean spotted fever showed that a 2-day course of doxycycline or ciprofloxacin was effective, and all participants were cured. Those treated with doxycycline produced more rapid defervescence.[161]

Brucellosis is typically treated with a 6-week course of doxycycline 100 mg orally twice daily with either streptomycin 15 mg/kg intramuscularly daily for the first 2 to 3 weeks or rifampin 600 to 900 mg daily for 6 weeks. This has been the long-standing recommendation of the World Health Organization and is still recommended as first-line therapy for brucellosis without serious complications.[164] However, the regimen of doxycycline with streptomycin has been shown to be superior with lower rates of relapse.[165] In a randomized controlled study looking at the combination of intramuscular gentamicin 5 mg/kg daily for 7 days with doxycycline versus standard doxycycline-streptomycin therapy, both arms were equivalent.[166] The addition of levofloxacin to the combination of doxycycline and rifampin for acute or subacute brucellosis may increase its efficacy in terms of lowering relapse rates within 6 months after stopping therapy, but not in terms of the rates of therapeutic failure after 6 weeks of therapy.[167] Complications of brucellosis, such as spondylitis, need to be treated for at least 12 weeks.[168]

Q fever, caused by *Coxiella burnetii,* ranges from a self-limiting febrile illness to difficult-to-treat endocarditis. Treatment with a tetracycline must begin within 2 days of symptom onset to become effective.[169] Doxycycline has been shown to reduce the duration of fever slightly better than tetracycline.[170] Recommended therapy in acute disease is doxycycline 100 mg orally twice daily for 14 days.[171] Patients with Q fever meningoencephalitis may respond to a 21-day course of doxycycline.[172] Patients with preexisting valvular heart disease who contract acute Q fever are at risk of developing endocarditis, reportedly at a rate of 39%.[173] Therapy with doxycycline and hydroxychloroquine for 1 to 15 months has been shown to reduce the risk of endocarditis. This observation has led the authors to recommend a 12-month course of dual therapy in such at-risk individuals.[173] Doxycycline 100 mg twice daily with hydroxychloroquine 200 mg three times a day is also typically used in treatment of Q fever endocarditis. This regimen was shown to result in fewer relapses than in patients treated with doxycycline combined with ofloxacin. In the doxycycline with hydroxychloroquine group, relapse occurred in two patients who were treated for 12 months, whereas no relapse occurred in patients who were treated for at least 18 months.[174]

Melioidosis, a *B. pseudomallei* infection, is usually treated initially with intravenous ceftazidime. After the induction phase, maintenance treatment is given for 12 to 20 weeks with a multidrug regimen. In an open-label, randomized study looking at chloramphenicol, doxycycline, and trimethoprim-sulfamethoxazole (TMP-SMX) versus doxycycline and TMP-SMX, the latter regimen was just as effective and better tolerated than the traditional four-drug group.[175] However, when the traditional four-drug regimen was compared with doxycycline monotherapy, doxycycline was inferior.[176]

Doxycycline has also been studied in diseases with limited therapeutic options. In a randomized study of 231 patients with dengue hemorrhagic fever, the group treated with 7 days of doxycycline had a 46% lower mortality compared with standard supportive care alone. Administration of doxycycline resulted in a significant decrease in levels of tumor necrosis factor and interleukin 6.[177] No effective treatment has yet been found for Creutzfeldt-Jakob disease (CJD). Data regarding the efficacy of doxycycline for CJD have been conflicting, but further study may be warranted.[178,179]

In the era of multidrug-resistant (MDR) gram-negative infections, minocycline has garnered recent interest owing to the limited treatment options for these organisms. Successful outcomes have been reported for the treatment of MDR *Acinetobacter,* carbapenem-resistant *Klebsiella pneumoniae,* and *S. maltophilia*.[180–182]

Acne Vulgaris

Acne vulgaris is a common adolescent disease usually treated with topical keratolytics for mild disease. Both doxycycline and minocycline are used for more severe disease as a way of treating patients with *Cutibacterium (Propionibacterium) acnes*–infected sebaceous glands in hair follicles. Antibiotics are usually prescribed for an average of 6 months and should be given for at least 2 months before consideration is given to switching antimicrobials because of poor therapeutic response.[183] In a randomized placebo-controlled study, minocycline 1 mg/kg daily over 12 weeks significantly reduced the number of inflammatory lesions compared with placebo.[184] This usage had raised concern for tetracycline resistance in the patient and in the population.

Antiinflammatory Uses

The tetracyclines have also drawn interest for their antiinflammatory properties. In a randomized study of 66 patients with early seropositive rheumatoid arthritis, initial therapy with methotrexate (MTX) plus doxycycline was superior to treatment with MTX alone. The therapeutic responses to low-dose (20 mg twice daily) and high-dose doxycycline (100 mg twice daily) were similar, suggesting that the antimetalloproteinase effects of doxycycline were more important than the antibacterial effects.[185] Minocycline has also been shown to be safe and effective for patients with mild-to-moderate rheumatoid arthritis, or Takayasu arteritis.[186–188] Data regarding the efficacy of minocycline for multiple sclerosis are conflicting.[189,190]

Bioterrorism Prophylaxis

Doxycycline is active against potential bioterrorism agents, including *B. anthracis, Y. pestis, Francisella tularensis, C. burnetii,* and *Brucella* spp. Compared with the fluoroquinolones, doxycycline is much less expensive and appears to have similar efficacy in most scenarios on the basis of clinical case studies. As a result, doxycycline should be considered as a first-line antibiotic in the event of a bioterrorism attack.[191]

Mechanism of Resistance

Resistance to the tetracyclines developed soon after their clinical introduction. The first reported case was in 1953 in an isolate of *Shigella dysenteriae.*[192] Tetracycline-resistant isolates can currently be found among a wide range of organisms. Increased prevalence of tetracycline

resistance was documented among Enterobacteriaceae, *Staphylococcus, Streptococcus,* and *Bacteroides* species by the 1970s, and in *N. gonorrhoeae* by the mid-1980s.[8] On the other hand, obligate intercellular pathogens, such as *Chlamydia* and *Rickettsia* species, have not been demonstrated to have significant tetracycline resistance.[193]

Resistance has developed among many different bacterial species as a result of horizontal exchange of resistance genes. There have been 33 distinct tetracycline-resistant genes identified, called *tet* genes, and three oxytetracycline resistant genes identified, called *otr* genes. These are found primarily on mobile units such as plasmids and transposons.[8,193,194]

There are various mechanisms of resistance to the tetracyclines. In the clinical setting, resistance via active efflux pumps and the production of ribosomal protection proteins (RPPs) are the principal mechanisms. Resistance can also develop via enzymatic degradation, decreased drug permeability, and target mutation.[6]

The tetracycline efflux system contains 26 different classes of efflux pumps that are responsible for the export of tetracycline from the cell. The efflux occurs because of genes encoding proteins that are members of the major facilitator superfamily (MFS) group of integral membrane transporters.[195] The efflux pumps are integral membrane proteins that span the lipid bilayer of the inner cell membrane 12 to 14 times.[6] This results in the export of tetracycline from the cell through an energy-dependent process. The end effect is a reduction of intracellular concentration of tetracycline, resulting in ribosomal protection of the bacteria. These pumps can be found in both gram-positive and gram-negative bacteria and typically confer resistance to early-generation tetracyclines but not to doxycycline and minocycline.

RPPs protect the ribosomes from the action of tetracycline. Eleven different types of RPPs have been identified, spanning both gram-positive and gram-negative bacteria. *Tet*(O) and *tet*(M) are the most prevalent and widely studied of the RPPs.[6] The RPPs work by weakening the interaction of tetracycline with the ribosome, preventing tetracycline from binding.[196] Thus, protein synthesis continues on tetracycline release. This mechanism generates resistance to both first- and second-generation tetracyclines but not to the newer third-generation glycylcyclines. Tigecycline is able to effectively exhibit antibacterial activity against *tet*(M) RPPs, likely because of a stronger affinity to its ribosomal target.[197]

Newer methods of tetracycline resistance have been identified through mosaic derivatives of known tetracycline resistance genes and are products of the RPP group of resistance determinants. At least one part of the gene shares more than 80% homology with a known tetracycline resistance gene; the other part shares homology with another known or new determinant.[6] Perhaps the best described example is from a ribosomal protection gene *tet*(32) isolated from *Clostridium* strain K10. This gene shares 60% identity with *tet*(O).[198]

A less common method of tetracycline resistance is a result of drug inactivation by tetracycline inactivators. In the entire tetracycline resistome, only three genes have been associated with tetracycline enzyme inactivation: *tet*(X), *tet*(34), and *tet*(37).[6] The first discovered was *tet*(X) in 1989 from a strain of *B. fragilis* that conferred resistance to *E. coli* when cells with the gene were grown aerobically.[199] The gene *tet*(X) inactivates tetracycline by selectively adding a hydroxyl group to the C-11a position of the antibiotic, which causes an unstable compound that undergoes nonenzymatic decomposition to a black polymer.[200] *Tet*(X) confers resistance to first- and second-generation tetracyclines and to tigecycline. *Tet*(X) uses nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of magnesium and converts tigecycline to 11a-hydroxytigecycline, which has a weakened ability to inhibit protein translation.[201]

Less common methods of tetracycline resistance include decreased drug permeability and target mutation. Tetracyclines are able to pass through the lipopolysaccharide-containing outer membrane of gram-negative bacteria by forming a magnesium complex followed by passage via porin channels. *E. coli* is able to overexpress the global activator protein MarA. This both induces the MDR efflux pump AcrAB and downregulates synthesis of the porin channel OmpF. The net effect reduces tetracycline uptake and accumulation in the cell.[202] Target modification has been shown in mutations of the 16S-rRNA of *H. pylori.* Studies have shown substitutions of nucleotides at positions 926, 927, and 928 in tetracycline-resistant isolates of *H. pylori*.[203,204] These substitutions can have a cumulative effect on the level of tetracycline resistance.

Adverse Reactions

General

As a class, the tetracyclines are generally well tolerated. A systematic review of studies between 1966 and 2003 summarized the adverse events (AEs) of doxycycline and minocycline. A total of 130 and 333 AEs were noted in published case reports of doxycycline and minocycline, respectively. In 24 doxycycline clinical trials ($n = 3833$) and 11 minocycline trials ($n = 788$), the ranges in incidence of AEs were 0% to 61% and 11.7% to 83.3%, respectively. The most common AEs encountered with doxycycline were gastrointestinal. Central nervous system and gastrointestinal AEs were most common with minocycline. The incidence of AEs with either drug is very low, but doxycycline had fewer reported AEs.[205]

In a more recent French review, adverse drug reactions (ADRs) of the tetracyclines were reviewed in studies performed between 1985 and 2007. Minocycline-associated ADRs were more serious and were reported more frequently than for the other tetracyclines. Minocycline and doxycycline ADR patterns differed. With doxycycline, gastrointestinal disorders (especially esophageal lesions) predominated. Intracranial hypertension and hepatic disorders were primarily reported with minocycline. Autoimmune disorders, drug reaction with eosinophilia and systemic symptoms, and other hypersensitivity reactions were also more frequent with minocycline. These findings led to the recommendation that minocycline should no longer be considered first-line therapy for inflammatory skin disorders, especially acne.[206]

Gastrointestinal Side Effects

As a class, tetracyclines commonly cause nausea, vomiting, diarrhea, heartburn, and epigastric pain. As stated earlier, gastrointestinal side effects are clearly the most common type of side effect of doxycycline, including pill esophagitis. Prolonged retention of the capsule in the esophagus, along with the high acidity of doxycycline in solution, is the likely cause of esophageal ulceration, and patients should drink at least 100 mL of water while standing upright for at least 90 seconds.[207,208] Patients with esophageal strictures should not take doxycycline. Diarrhea may occur with doxycycline, but there appears to be a reduced risk of CDI.[123,124] Minocycline also commonly causes nausea, but vomiting, diarrhea, and esophageal ulcerations occur much less frequently.[205,209]

Photosensitivity and Hyperpigmentation

A photosensitive rash commonly occurs in sun-exposed areas of patients taking tetracyclines.[205,206] This is caused by radiant-exposure–dependent inhibition of cellular incorporation of thymidine.[210] This reaction occurs as a result of drug accumulation in the skin and is phototoxic. This may occur shortly after exposure to the sun and can persist for a few days after the drug is discontinued. Severe cases may be associated with edema, papules, vesiculations, and onycholysis.[211]

Hyperpigmentation of various body parts has been well described with the tetracyclines, particularly minocycline.[205] Different types of cutaneous pigmentation have been described. It can cause a blue-black discoloration that occurs at sites of prior inflammation or scarring, a blue-black or gray localized macular pigmentation on normal arm skin, and a muddy-brown pigmentation predominantly on sun-exposed areas.[212,213] Blue-black discoloration of gums secondary to bone pigmentation that is visible through nonpigmented oral mucosa has been described with long-term use of minocycline and appears to be permanent.[214–216] Asymptomatic black pigmentation of the thyroid associated with minocycline has also been reported.[217,218]

Teeth and Bone

Tetracyclines deposit in teeth and bones as a result of chelation of tetracycline with calcium. The teeth can become stained owing to the formation of tetracycline-calcium orthophosphate complexes that darken with sun exposure.[219,220] This phenomenon is mostly cosmetic, but it may also cause demineralization and enamel hypoplasia leading to tooth decay.[221] Enamel hypoplasia has been most commonly described

in premature infants.[222] Doxycycline has a lower potential for teeth and bone deposition than the other tetracyclines because of its lower avidity for calcium. The degree of tooth discoloration is dependent on the total amount of tetracycline product administered.[223] Children receiving tetracycline early in life tend to have deposition in their deciduous teeth. This can also occur in developing fetuses when their mother receives tetracycline during pregnancy, particularly after the 25th week of gestation.[224] Tetracycline has also been noted to inhibit bone growth in infants receiving the drug. Premature infants displayed a 40% reduction of normal fibula skeletal growth after receiving tetracycline.[225] Fortunately, this appears to be reversible after drug discontinuation.

Hepatotoxicity

Even though hepatotoxicity is rarely associated with tetracycline use, it is potentially fatal. Hepatotoxicity has been well described with high-dose intravenous preparations of tetracycline.[226] This led to the withdrawal of intravenous tetracycline from the US market. Rarely, acute symptomatic hepatitis requiring hospitalization may develop with prolonged use of oral tetracycline over a period of 10 days.[227] Doxycycline does not appear to have the same side-effect profile and is rarely associated with significant liver toxicity.[16,228]

Nephrotoxicity

In the setting of impaired renal function, the tetracyclines can exacerbate renal malfunction by inhibiting protein synthesis. This causes a catabolic effect on amino-acid metabolism, leading to azotemia, hyperphosphatemia, and acidosis.[229] Expired tetracycline has been shown to produce a reversible Fanconi-like syndrome with renal tubular acidosis, likely due to citric acid, which accelerates the deterioration of stored tetracycline.[230] Current formulations of tetracycline have been modified so that they do not contain citric acid. Doxycycline is considered safe to use in the setting of renal impairment; it does not accumulate in the serum because its gastrointestinal excretion increases.[14] The side effect of demeclocycline, which causes nephrogenic diabetes insipidus, is used to treat the chronic syndrome of inappropriate antidiuretic hormone secretion.[7]

Neurotoxicity

Central nervous system effects have been described the most with minocycline. Minocycline has been noted to cause reversible dizziness, vertigo, tinnitus, and lack of concentration. Vestibular side effects have been reported to be higher in women (70.4%) than in men and are usually seen by the third day.[209] Pseudotumor cerebri, or idiopathic intracranial hypertension, has been noted with prolonged use of minocycline, and with tetracycline and doxycycline.[231–235] Symptoms may occur within 2 weeks to 6 months of therapy. Withdrawal of the offending antibiotic and treatment for increased intracranial pressure should lead to resolution of the pseudotumor cerebri syndrome, but visual field loss may persist.

Hypersensitivity Reactions

Hypersensitivity reactions are uncommon but appear to occur more frequently with minocycline.[206] They can include urticaria, facial edema, drug-induced autoimmune disease, and rarely anaphylaxis. Minocycline has been associated with drug-induced autoimmune disorders, the most common being drug-induced lupus.[236] Rare cases of anaphylaxis have been reported with administration of tetracycline to a penicillin-allergic patient.[237] Stevens-Johnson syndrome due to doxycycline is also rare but has been reported.[238] Cross-allergic reaction occurs between different drugs in this class. A patient with a hypersensitivity reaction to one antibiotic should be considered hypersensitive to all tetracyclines.

Teratogenicity

The tetracyclines are able to cross the placenta into the fetus. In a review of 18,515 pregnancies with congenital abnormalities, 0.3% were exposed to doxycycline. This was slightly higher than 0.19% of the 32,804 pregnancies without congenital abnormalities that were exposed to doxycycline. The conclusion of the study was that doxycycline poses little, if any, teratogenic risk to a fetus and there should be no contraindication to its use in pregnancy.[239] A more recent study of 1795 pregnancies exposed to doxycycline showed that there was no increase in risk of fetal abnormalities.[240] The tetracyclines are still generally avoided in pregnancy owing to their potential to stain teeth and cause enamel hypoplasia.

Drug and Food Interactions

Significant interactions between tetracyclines and other drugs or food are summarized in Table 26.3.

GLYCYLCYCLINES

Tigecycline

Glycylcyclines are a novel class of antibacterial drugs that have been developed to combat the emergence of resistant organisms. Tigecycline is the first member of the class to be approved by the FDA, in June 2005. It was originally approved for the treatment of complicated skin and skin structure infections (cSSSIs) and complicated intraabdominal infections (cIAIs) based on noninferiority studies.[241,242] In March 2009, tigecycline was approved for the treatment of community-acquired bacterial pneumonia based on comparable cure rates in patients treated with levofloxacin.[243,244] Tigecycline is considered bacteriostatic and is active in vitro against a broad range of resistant aerobic and anaerobic bacteria. The FDA issued a warning regarding an increased risk of death with tigecycline compared with other antibiotics used to treat similar infections based on the pooled analysis of 13 clinical trials.[245] In 2013 the FDA approved a new boxed warning about this risk of death and warned health care professionals to reserve tigecycline for use in situations in which alternative treatments are not suitable.[246] In general, the deaths appear related to worsening or complications of the infection or underlying comorbidities. Study-level and patient-level analyses have identified that patients in the hospital-acquired pneumonia (HAP) trial, particularly those with ventilator-associated pneumonia (VAP) with baseline bacteremia, were at a higher risk of clinical failure and mortality.[247]

Structure and Mechanism of Action

Tigecycline is a semisynthetic derivative of minocycline. It has an *N*-alkyl-glycylamido moiety attached to the 9-position of minocycline.[248] (See Fig. 26.1 for molecular structure.) The design is based on the premise that a peptide substituent would enhance ribosomal permeation and binding. The 9-glycyl substitution results in steric hindrance that enables tigecycline to overcome the two major types of tetracycline resistance: tetracycline-specific efflux pumps and ribosomal protection.[249]

Tigecycline's antibacterial mechanism of action is similar to that of older tetracyclines. It works by inhibiting bacterial protein synthesis by binding to bacterial 30S ribosomal subunits, ultimately blocking entry of aminoacyl transfer RNA molecules into the A site of the ribosome. This prevents amino acids from incorporating into elongating peptide chains, thus inhibiting protein synthesis.[249,250] Like other tetracyclines, tigecycline is considered bacteriostatic because its interaction with the ribosome is reversible.[8] Because glycylcyclines bind five times more strongly to the ribosome than tetracyclines, they are able to overcome the ribosomal protection mechanism of the tetracycline resistome.[251,252]

Pharmacology

Administration and Dosing

Tigecycline is available only in intravenous formulation owing to its poor oral absorption. The recommended regimen is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions should be administered over approximately 30 to 60 minutes. According to the package insert, the recommended duration of treatment for cSSSIs or for cIAIs is 5 to 14 days. The recommended duration for treatment of community-acquired bacterial pneumonia is 7 to 14 days. It has not been studied in children younger than 18.[253]

In patients with renal impairment, no dose adjustment is necessary. In a pooled pharmacokinetic evaluation of tigecycline in healthy adult volunteers and in those with renal impairment, tigecycline had mostly linear pharmacokinetics across all dose ranges. Tigecycline is also not significantly removed by hemodialysis.[254]

TABLE 26.3 Significant Food-Drug and Drug-Drug Interactions With Tetracyclines

INTERACTING AGENT	EFFECT	COMMENTS
Food	**Tetracycline** Food may reduce absorption by 50% **Doxycycline** Absorption may be reduced by up to 20% when taken with food or milk **Minocycline** Absorption may be reduced by up to 20% when taken with food or milk	Bioavailability is 60%–80% when taken on an empty stomach Food effect not clinically significant Food effect not clinically significant
Divalent or trivalent cations: aluminum, calcium, magnesium, iron, zinc	Significant reduction of all tetracycline absorption	Should not be administered concurrently with foods or drugs containing divalent or trivalent cations (i.e., antacids, sucralfate, didanosine, multivitamins)
Kaolin and pectin	Significant reduction of tetracycline absorption	
Bismuth subsalicylate	Significant reduction of tetracycline absorption	Separate administration of tetracycline from divalent or trivalent cations by 2 hours
Sodium bicarbonate	May decrease absorption of tetracycline	
Cimetidine	Decreased tetracycline absorption	Effect not clinically significant
Carbamazepine, phenytoin, barbiturates	Decreased half-life of doxycycline	Increases hepatic metabolism
Chronic ethanol ingestion	Decreased half-life of doxycycline but not tetracycline	Possible mechanism: induction of hepatic microsomal enzymes
Methoxyflurane or fluorinated anesthetic	Nephrotoxicity when administered with tetracycline agents	
Diuretics	Increased blood urea nitrogen	Volume depletion may increase the nephrotoxic effects of tetracycline by unknown mechanisms
Oral anticoagulants	Increased risk of bleeding	Tetracyclines may impair utilization of prothrombin and may decrease vitamin K production by intestinal bacteria; tigecycline decreases warfarin clearance, although a study found no effect in healthy volunteers
Oral contraceptives	Reduced levels when administered with tetracyclines	Women should use an additional (mechanical) form of birth control Possible mechanism: reduction in bacterial hydrolysis of conjugated estrogen in the intestine
Antiinfectives	May reduce antimicrobial activity of aminoglycosides and penicillins	Rare reports of in vitro antagonism Some clinicians recommend that the drugs not be used concomitantly

In patients with mild-to-moderate hepatic impairment (Child-Pugh A and B), no dose adjustment is necessary. In patients with severe hepatic impairment (Child-Pugh C), the recommended regimen is an initial dose of 100 mg, followed by a reduced maintenance dose of 25 mg every 12 hours. These patients should be treated with caution and monitored closely. In a study looking at various stages of liver dysfunction, patients with moderate liver disease had systemic clearance reduced by 25%, and the half-life was increased by 23%. In patients with severe liver disease, systemic clearance was decreased by 55% and the half-life was increased by 43%.[255]

There do not appear to be any significant differences in tigecycline pharmacokinetic parameters on the basis of age, sex, or weight. Therefore, no dose adjustment appears necessary.[256]

Absorption and Bioavailability

Tigecycline has limited oral bioavailability; hence, it is available only in intravenous preparations. Food does not significantly alter pharmacokinetics and may reduce the nausea and vomiting seen as a side effect. The half-life of tigecycline ranges from 37 to 67 hours.[257]

Drug Distribution

In vitro plasma protein binding of tigecycline is 71% to 89%, and the volume of distribution is 7 to 10 L/kg, indicating extensive distribution into the tissues.[257] In a 100-mg single-dose study of patients undergoing elective surgery or a medical procedure for tissue extraction, various tissue concentrations were measured. The respective mean and median concentration values of tigecycline in serum immediately after the end of a 100-mg infusion were 1.94 and 1.32 mg/L. Subsequent serum concentrations of tigecycline gradually declined to mean values of 0.22, 0.19, 0.11, and 0.07 mg/L at approximately 4, 8, 12, and 24 hours, respectively. Tissue penetration, expressed as the ratio of area under the curve $(AUC)_{0-24h}$ in tissue or body fluid to serum, was 537 for bile, 23 for gallbladder, 2.6 for colon, 2.0 for lung, 0.41 for bone, 0.31 for synovial fluid, and 0.11 for CSF.[258] In a separate study of subjects without infections undergoing elective orthopedic procedures, multiple doses of tigecycline were shown to result in bone-to-serum ratios of approximately 4.77, showing penetration into bone.[259] After standard dosing to 33 healthy volunteers, the tigecycline AUC_{0-12h} in alveolar cells was 78-fold higher than the AUC_{0-12h} in the serum. In epithelial lining fluid, the AUC_{0-12h} was about 32% higher than in the serum.[253] In the urine, after a 100-mg dose of tigecycline, urinary concentrations were about 0.3 μg/mL.[260] Clinical trials in urinary tract infections were abandoned on precompletion review because there was limited urinary recovery of active drug.[261] Like the earlier-generation tetracyclines, tigecycline displays a time-dependent killing pattern and exhibits a considerable postantibiotic effect.[262]

Drug Elimination

The primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Using radiolabeled carbon 14 (^{14}C)-tigecycline, studies have shown elimination primarily by the liver via biliary excretion of unchanged tigecycline in the feces (59%). Glucuronidation and renal excretion of unchanged tigecycline are secondary routes. Thirty-two percent of tigecycline is eliminated in the urine.[257,263]

Antimicrobial Activity

Tigecycline has antibacterial activity against a wide variety of aerobic and anaerobic bacteria. For reference to MIC cutoff values for various clinically relevant species, see Table 26.4.

Gram-Positive Bacteria

Tigecycline is active against many *Staphylococcus, Enterococcus,* and *Streptococcus* species, including organisms resistant to many other

TABLE 26.4 Overview of the MIC_{50} and MIC_{90} Ranges, and the Wild-Type Cutoff Values for Various Species That Are Clinically Relevant for Tigecycline Use

	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	RANGE (μg/mL)	EUCAST WILD-TYPE CUTOFF
Gram-Positive Bacteria				
Staphylococcus aureus, methicillin-resistant	0.12–0.25	0.25–0.5	0.06–1	0.25
S. aureus, methicillin-sensitive	0.12	0.12–0.5	≤0.06–1	0.25
Staphylococcus epidermidis, methicillin resistant	0.12–0.25	0.25–0.5	≤0.06–2	0.5
S. epidermidis, methicillin-sensitive	0.12–0.25	0.25–0.5	0.06–2	0.5
Enterococcus faecalis, vancomycin susceptible	≤0.06–0.12	0.12–0.25	≤0.06–2	0.25
Enterococcus faecium, vancomycin susceptible	≤0.06	≤0.06–0.25	≤0.06–2	0.25
E. faecium, vancomycin resistant	≤0.06	≤0.06–0.12		0.25
Streptococcus pyogenes	0.06	0.06–0.12	0.06–0.5	0.125
Streptococcus agalactiae	0.03–0.06	0.12–0.25	0.03–1	0.25
Streptococcus pneumoniae	≤0.03–0.12	0.06–0.5	≤0.06–1	0.125
Gram-Negative Bacteria				
Enterobacteriaceae	0.5	1	0.04–16	—
Enterobacter spp.	0.5	1–2	0.06–8	—
Enterobacter cloacae	0.5–1	1–2	0.5–16	2
Enterobacter aerogenes	0.5–1	1–2	0.06–16	2
Escherichia coli	0.12–0.25	0.25–0.5	0.03–4	1
Haemophilus influenza	0.12–0.5	0.25–1	≤0.008–2	1
Klebsiella spp.	0.5	1–2	0.5–8	2 *(K. pneumoniae)*
Klebsiella pneumoniae ESBL+	1	2	0.12–8	—
Moraxella catarrhalis	0.06–0.12	0.12–0.25	≤0.03–0.5	0.125
Morganella morganii	2	4	1–8	8
Proteus spp.	4	4–8	1–16	4/8
Serratia spp.	1–2	1–4	0.5–16	4
Stenotrophomonas maltophilia	0.38–1	1.5–4	0.25–8	4
Pseudomonas aeruginosa	8–16	16–≥32	0.12–64	64
Acinetobacter spp.	0.5–3	1–6	0.03–8	—
Anaerobic Bacteria				
Bacteroides fragilis group	0.5–1	0.5–8	0.06–32	—
Clostridioides difficile (formerly *Clostridium difficile*)	0.06–0.12	0.06–0.25	≤0.06–2	—
Clostridium perfringens	0.12	1	0.06–2	—
Fusobacterium spp.	0.03–0.12	0.06–0.12	≤0.015–0.25	—
Peptostreptococcus spp.	0.06	0.06–0.125	0.06–0.12	

ESBL, Extended-spectrum β-lactamase; *EUCAST,* European Committee on Antimicrobial Susceptibility Testing; *MIC,* minimal inhibitory concentration.
From Nabuurs-Franssen M, Mouton JW. Tigecycline. In: Grayson ML, ed. Kucers' The Use of Antibiotics. 6th ed. Boca Raton, FL: CRC Press; 2010:881–892.

classes of antibiotics. Among *S. aureus,* tigecycline has shown potent activity among both methicillin-sensitive and methicillin-resistant strains.[264–266] Tigecycline has also been shown to be highly active against community-acquired MRSA strains as seen in a study of 1989 isolates with a susceptibility rate of 98.2%.[267] In a European survey of common skin and skin structure pathogens, all MRSA isolates were susceptible to tigecycline.[268] *Staphylococcus epidermidis* has also been shown to be susceptible to tigecycline, including strains that are erythromycin resistant.[269]

Tigecycline is also highly active against *Enterococcus* spp., including strains resistant to vancomycin. In a study of 97 vancomycin-resistant isolates, tigecycline was equally active against all VanA, VanB, and VanC phenotypes of glycopeptide resistance of enterococci.[270] In the Tigecycline Evaluation and Surveillance Trial (TEST) program, which took place from 2004 to 2009 and looked at various antimicrobials against *Enterococcus faecalis* and *Enterococcus faecium,* all 2068 isolates of *E. faecalis* were susceptible to tigecycline in various European countries. Only 2 out of 893 (0.2%) of *E. faecium* isolates were resistant to tigecycline.[271] In a Korean study, 4 out of 2005 (0.2%) of vancomycin-resistant enterococci (VRE) isolates were resistant to tigecycline.[272]

Streptococci have also been shown to be highly susceptible to tigecycline, including bloodstream isolates of viridans-group streptococcal species.[273] Tigecycline has also shown excellent activity against β-hemolytic streptococci.[274] Tigecycline was twofold to fourfold more active than comparator agents against all 435 isolates of *S. pneumoniae* studied in the global TEST program, including those that were penicillin resistant and penicillin intermediate. Against the penicillin-susceptible *S. pneumoniae* isolates, tigecycline was less active than β-lactam agents.[275] In another study, tigecycline was noted to be bactericidal against 11 of 12 strains of *S. pneumoniae.*[276]

Tigecycline has also been shown to be highly active against *L. monocytogenes* and coryneform bacteria.[277]

Gram-Negative Bacteria

Tigecycline has good activity against most Enterobacteriaceae with the exception of most strains of *Proteus* spp., *Providencia* spp., and *Morganella* spp.[274,278,279] Enterobacteriaceae that have developed resistance to tetracycline remain susceptible to tigecycline because it remains stable and largely unaffected by the commonly occurring efflux and ribosomal protection resistance mechanisms. In a large global study, tetracycline-resistant populations demonstrated only modest decreases in potency to tigecycline, which appeared to be species dependent (up to twofold only for *E. coli*, *Salmonella* spp., *Shigella* spp., and *Pantoea agglomerans* and up to fourfold for *Klebsiella* spp., *Enterobacter* spp., and *Citrobacter* spp.[280] Other resistance mechanisms, such as extended-spectrum β-lactamase (ESBL) production, AmpC hyperproducers, carbapenemase-producing Enterobacteriaceae, serine- and metallo-β-lactamases, fluoroquinolone resistance, fluoroquinolone/ampicillin resistance phenotype, fluoroquinolone/TMP-SMX resistance phenotype, and isolates with MDR phenotypes, do not have an influence on the MIC value of tigecycline.[280–284]

Tigecycline has good activity against most nonfermenting gram-negative bacilli with the notable exception of *Pseudomonas aeruginosa*. It remains one of the most active agents against *Acinetobacter* spp.[275,278,285] Although most studies have noted a high level of *Acinetobacter* spp. susceptibility to tigecycline, one study in Israel noted that of 82 isolates, 66% were resistant, 12% were intermediate, and just 22% were susceptible to tigecycline.[286] In the United States, most antimicrobial agents have shown reduced susceptibility to *A. baumannii* over recent years, including tigecycline.[285] *S. maltophilia* has been shown to be highly susceptible to tigecycline in vitro. In a large global survey of 1586 isolates, 95.5% were susceptible to tigecycline, which was second only to TMP-SMX (96%).[287]

In another global study, 1220 strains of *H. influenzae,* 495 strains of *Moraxella catarrhalis,* and 17 strains of *N. meningitidis* were all susceptible to tigecycline.[288] *Brucella melitensis* is highly susceptible to tigecycline both in vitro and in blood and bone marrow cultures of adult patients with acute brucellosis.[289–291] Tigecycline has reduced activity against *B. cepacia*.[252]

Anaerobic Bacteria

Tigecycline is active against most gram-positive and gram-negative anaerobes. In vitro activities of tigecycline were tested against 831 isolates of the *B. fragilis* group representing all of the species within the group. Tigecycline was more active than clindamycin, minocycline, and cefoxitin and less active than imipenem or piperacillin-tazobactam against all isolates of the *B. fragilis* group.[292] In the European TEST program looking at *Bacteroides, Prevotella, Anaerococcus, Clostridium, Finegoldia,* and *Peptostreptococcus,* the lowest MIC values were noted for meropenem and tigecycline. Of note, tigecycline showed the lowest MIC_{90} against *C. difficile* (0.25 mg/L).[293]

Atypical Bacteria

Tigecycline is highly active against *C. pneumoniae, C. trachomatis, M. pneumoniae,* and *M. hominis*.[84,294] It is less active against *U. urealyticum* than tetracycline, with an MIC_{90} of 8 μg/mL.[294] In a guinea pig model, tigecycline was shown to be as effective as erythromycin against *L. pneumophila,* but the drug was inactivated by test medium that confounded susceptibility data. Tigecycline prevented death in the study, but treated guinea pigs were noted to have residual bacterial concentrations in the lungs, suggesting that tigecycline may not be the drug of choice for severe legionnaires' disease, and prolonged therapy would be required.[295]

Mycobacterium and *Nocardia*

The rapidly growing mycobacteria (RGM) appear to be highly sensitive to tigecycline. In two separate studies, every RGM isolate, mostly consisting of *M. fortuitum, M. abscessus,* and *M. chelonae,* was susceptible to tigecycline.[96,296] All slowly growing nontuberculous mycobacteria, including *M. avium* complex, *Mycobacterium lentiflavum, M. marinum,* and *M. kansasii,* are resistant to tigecycline.[96] The in vitro activity against *M. tuberculosis* appears poor.[297] Tigecycline has modest activity against *Nocardia* spp., with an MIC_{90} of 4 μg/mL. By comparison, minocycline has an MIC_{90} of 2 μg/mL.[102]

Clinical Uses

Tigecycline is currently FDA approved for three indications: treatment of cSSSIs, cIAIs, and community-acquired bacterial pneumonia. It is also used off label for many other disease processes.

Skin and Skin Structure Infections

Several clinical studies have compared tigecycline versus a combination of vancomycin and aztreonam for up to 14 days for the treatment of skin and skin structure infections. Similar results have been seen across studies that have shown tigecycline to be noninferior. Among the clinical modified intention-to-treat populations, tests of cure were between 73.3% and 84.3% for tigecycline and between 66.6% and 86.9% for the vancomycin-aztreonam group. Tests of cure for the clinically evaluable populations were 78.6% to 89.8% and 75.8% to 95%, respectively. Increased nausea and vomiting was consistently seen in the tigecycline group, whereas rash and elevated transaminases were consistently seen in the vancomycin-aztreonam group.[241,298–301] In the largest study, no differences were noted in clinical cure rates in patients who were bacteremic (86% vs. 87.5%). Tigecycline had equal efficacy in patients with monomicrobial and polymicrobial infections.[241]

A phase III, randomized, double-blind trial was conducted in subjects with diabetic foot infections with and without osteomyelitis comparing a 150-mg once-daily regimen of tigecycline versus ertapenem with or without vancomycin. For the clinically evaluable population at test-of-cure assessment, 77.5% of tigecycline-treated participants and 82.5% of ertapenem-treated participants with or without vancomycin were cured. Corresponding rates for the clinical modified intention-to-treat population were 71.4% and 77.9%, respectively. Tigecycline did not meet the criteria for noninferiority. Clinical cure rates in the substudy were low (<36%) for a subset of patients with osteomyelitis treated with tigecycline. Higher rates of nausea and vomiting with higher discontinuation rates were observed for tigecycline in this trial than in other phase III studies.[302]

Intraabdominal Infections

Tigecycline is an attractive option to treat cIAIs because its broad spectrum of activity is favorable against a potentially polymicrobial infection. In two large studies of cIAIs, tigecycline was compared with imipenem-cilastatin for 5 to 14 days of treatment. Complicated appendicitis was the most common infection, followed by complicated cholecystitis. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were similar, and less than 4% of patients had scores over 15. Clinical cure rates were 86.1% for tigecycline and 86.2% for imipenem-cilastatin, meeting noninferiority criteria. There was no difference in cure rates between the two therapies for monomicrobial versus polymicrobial infections. Clinical cure rates for bacteremia were also similar (82% vs. 80%, respectively). The most common organisms were *E. coli*, *Streptococcus anginosus* group, and *B. fragilis*. Only vancomycin-susceptible isolates were included. Eradication rates were similar for ESBL-producing bacteria. Nausea and vomiting were more frequent in the tigecycline group.[242,303] In a more recent Chinese study comparing the same two therapies for up to 2 weeks, 86.5% (45/52) of tigecycline and 97.9% (47/48) of imipenem-cilastatin–treated patients were cured at the test-of-cure assessment (12–37 days after therapy).[304]

Two other studies have compared tigecycline with a combination of ceftriaxone plus metronidazole for cIAIs. Clinical cure rates were between 70.4% and 81.8% in the tigecycline group and 74.3% and 79.4% in the ceftriaxone-metronidazole group, again displaying noninferiority.[305,306]

Respiratory Tract Infections

Tigecycline has been approved for the treatment of community-acquired bacterial pneumonia. It has been compared with levofloxacin in multiple studies with treatment durations between 7 and 14 days and Fine Pneumonia Severity Index scores typically from II to IV. Among the clinical modified intention-to-treat populations, test-of-cure results were between 78.7% and 84.4% for tigecycline and between 77.8% and 82.1% for the levofloxacin group. Test-of-cure results for the clinically evaluable populations were 88.9% and 90.6% and 85.3% and 87.2%, respectively.

All trials met noninferiority criteria for tigecycline. As with other clinical trials, more patients tended to have nausea and vomiting in the tigecycline groups.[243,244,307,308]

Tigecycline has also been looked at for treating VAP and HAP. In a retrospective review of 117 patients with VAP treated with tigecycline, 74 (63%) were determined by the physician to have clinical success. About half of the patients had a microbiologic diagnosis, and of those the most common organisms were *Acinetobacter* spp. (69%) and MRSA (22%). Eighty-four percent of the cases with *Acinetobacter* spp. were carbapenem resistant. Global mortality proportion was 33%.[309] In a phase III randomized controlled trial involving 945 patients, tigecycline was compared with imipenem-cilastatin for the treatment of HAP. Cure rates were 67.9% for tigecycline and 78.2% for imipenem-cilastatin in the clinically evaluable group and 62.7% and 67.6% in the clinical modified intention-to-treat group, respectively. A statistical interaction occurred between VAP and non-VAP subgroups, with significantly lower cure rates in tigecycline-treated VAP patients compared with imipenem; in non-VAP patients, tigecycline was noninferior to imipenem. Overall mortality did not differ between the tigecycline (14.1%) and imipenem-cilastatin regimens (12.2%), although more deaths occurred in VAP patients treated with tigecycline than imipenem-cilastin.[310] In a subsequent phase II study, the safety and efficacy of two higher doses of tigecycline (150 mg followed by 75 mg every 12 hours or 200 mg followed by 100 mg every 12 hours) were compared with imipenem-cilastatin in participants with HAP. In the clinically evaluable population, the rate of clinical cure with tigecycline 100 mg (17/20, 85.0%) was numerically higher than with tigecycline 75 mg (16/23, 69.6%) and imipenem-cilastatin (18/24, 75.0%). No new safety signals with the high-dose tigecycline were identified.[311] Further studies with this higher-dose regimen are needed.

Other Uses

Tigecycline is also used for many off-label indications. In an early-use registry of 113 patients, 22% received tigecycline for approved indications and 78% for off-label indications (56% with scientific support and 22% with limited or without any scientific support).[312]

Although there are no randomized prospective trials looking at the use of tigecycline for bacteremia, secondary bacteremia in prior clinical trials has been analyzed. Pooled data from subjects enrolled for treatment of cSSSI, cIAI, or CAP presenting with bacteremia from seven double-blind and one open-label trial of tigecycline compared with vancomycin-aztreonam, imipenem-cilastatin, levofloxacin, vancomycin, or linezolid were analyzed. A total of 170 subjects were identified, and clinical cure rates were 81.3% and 78.5% for tigecycline and the comparator, which did not achieve significance. Nine patients treated with tigecycline were noted to have persistent bacteremia, as compared with one in the comparator group.[313] Tigecycline, in a solution with *N*-acetylcysteine and heparin, was evaluated as a catheter-lock solution for catheter salvage in patients with hemodialysis catheter-associated bacteremia. Eighteen case patients received the catheter-lock solution for 14 days plus systemic antibiotic therapy. Treatment was successful for 15 (83%) of the 18 case patients within 90 days of follow-up.[314]

In critically ill patients who have developed bacterial infections with multidrug resistance, tigecycline remains an attractive option owing to its ability to maintain in vitro activity. A phase III, open-label, noncomparator study evaluated tigecycline in patients with selected serious infections caused by resistant gram-negative bacteria, patients with treatment failures who had received prior antimicrobial therapy, or patients unable to tolerate other appropriate antimicrobials. Infections included cSSSI, cIAI, CAP, HAP, VAP, and bacteremia (including catheter-associated bacteremia). Clinical cure rate was 72.2%, and the microbiologic eradication rate was 66.7%.[315] Another phase III study compared the safety and efficacy of tigecycline with vancomycin or linezolid in hospitalized patients with MRSA or VRE infections. Infections included cSSSI, cIAI, pneumonia, and bacteremia. For MRSA infection, clinical cure rates in the microbiologically evaluable population ($n = 117$) were 81.4% (70/86 patients) with tigecycline and 83.9% (26/31 patients) with vancomycin. Most infections were cSSSIs. There were only 15 patients enrolled with VRE, and the authors were not able to draw any conclusions.[316] In a report of 110 cancer patients who developed serious infections, 64% were noted to have a clinical response when treated with tigecycline (92% were treated in combination with an antipseudomonal agent). Interesting to note, more patients with bacteremia than pneumonia had clinical response (79% vs. 51%). Mortality rates of those with pneumonia were 44%, compared with 16% with bacteremia.[317] The combination of piperacillin-tazobactam and tigecycline was found to be more effective than piperacillin-tazobactam alone in febrile, neutropenic hematologic patients with cancer in an epidemiologic setting characterized by a high rate of MDR microorganisms.[318] In a prospective, observational study of adults with extensively drug-resistant *A. baumannii* bacteremia, increased 14-day mortality was observed with the combination of colistin-tigecycline compared with a colistin-carbapenem regimen. The excess mortality may have been restricted to the subgroup with higher tigecycline MICs (>2 mg/L).[319]

Clinical trials that have looked at use of tigecycline for urinary tract infections were abandoned at precompletion review because there was limited urinary recovery of active drug.[261] In a retrospective cohort study of carbapenem-resistant *K. pneumoniae* bacteriuria, tigecycline, polymyxin B, and an aminoglycoside were compared. The microbiologic clearance rate was 88% in the aminoglycoside cohort ($n = 41$), 64% in the polymyxin B cohort ($n = 25$), 43% in the tigecycline cohort ($n = 21$), and 36% in an untreated cohort.[320] Success with tigecycline for treating MDR *K. pneumoniae* and *A. baumannii* urinary tract infection or urosepsis has been reported with use of "high-dose" tigecycline, with initial doses between 200 and 400 mg and subsequent maintenance doses of 100 to 200 mg every 24 hours.[260]

Interest in using tigecycline for *C. difficile* infections (CDIs) has arisen owing to its in vitro activity and high stool concentrations. Currently, no clinical trials have evaluated tigecycline for the treatment of CDI. There have been multiple case reports of use of tigecycline (alone or in combination with other CDI therapies) for the treatment of CDI, with most having a successful outcome.[321–323] In a retrospective case-control study of severe CDI, 18 patients who received tigecycline (along with other CDI therapies) were compared with 26 similarly ill patients who did not receive tigecycline. There was no difference with regard to CDI survival, rates of colectomy, or relapse rates.[324]

Limited data exist regarding use of tigecycline for bone and joint infections. In the previously mentioned phase III study in diabetic foot infections with and without osteomyelitis, clinical cure rates in the substudy were low (<36%) for a subset of tigecycline-treated patients with osteomyelitis.[302] In a retrospective study of 15 patients with culture-negative pyogenic vertebral osteomyelitis, tigecycline was given as second-line empirical therapy. One patient dropped out because of severe nausea and vomiting. The other 14 patients were deemed to have had sustained clinical success.[325] Tigecycline was also evaluated in a retrospective case series of 19 patients with osteomyelitis. Five patients ceased therapy because of AEs. A sixth patient dropped out for unknown reasons. Eleven patients met the primary efficacy end point of clinical success.[326]

Treatment of infections with RGM can be difficult. The safety and efficacy of a tigecycline-containing regimen for salvage treatment of 52 patients with *M. abscessus* and *M. chelonae* was performed. Included patients had both lung and extrapulmonary infections. Tigecycline given for at least 1 month as part of a multidrug regimen resulted in improvement in over 60% of patients, including those with underlying cystic fibrosis, despite failure of prior antibiotic therapy. AEs were reported in over 90% of cases, the most common being nausea and vomiting.[327]

Mechanism of Resistance

Tigecycline remains active against bacteria that contain efflux-mediated resistance to tetracyclines. This is likely a result of the efflux pump's ineffectiveness in transporting tigeclycine out of the cell, or from the inability of tigecycline to induce efflux proteins.[328,329] There is also currently no evidence of gene mutations coding for RPPs for the *tet* family (*tet* M, O, S) for reduced susceptibility to tigecycline.

The most common intrinsic tigecycline resistance observed in *Proteus mirabilis* and *Morganella morganii* is drug recognition and upregulation by the AcrAB and MexAB-OprM efflux pumps, which typically confer MDR phenotypes.[330,331] Overexpression of these pumps is also associated with the development of resistance to other gram-negative bacteria.

P. aeruginosa is intrinsically resistant to tigecycline as a result of the MexXY multidrug efflux pump.[332]

The overexpression of mepA, a novel MATE family efflux pump, may contribute to decreased activity of tigecycline against *S. aureus*.[333]

Adverse Reactions

Gastrointestinal Side Effects

As with older tetracyclines, the most commonly reported adverse reactions to tigecycline are gastrointestinal related. As seen in multiple phase III clinical trials, nausea (26%) and vomiting (18%) were the most reported side effects.[241,242,253,298,334] The majority of these symptoms (95%) were mild to moderate and occurred after 1 to 2 days of therapy. The side effects are dose related; 100 mg was the highest dose tolerated in fasting healthy participants, and 200 mg was the highest dose tolerated with food.[257] Less-reported side effects are anorexia, dry mouth, dysgeusia, and loose stool.[281]

Hepatotoxicity and Pancreatitis

Transient elevations in transaminases and alkaline phosphatase levels have been seen.[335] However, in phase III clinical trials, the incidence of increased liver function test results was significantly lower with tigecycline than with comparator drugs.[241,243] Case reports of mild tigecycline-induced acute pancreatitis have also been reported.[336]

Other Side Effects

Other side effects reported from clinical trials that have an incidence between 2% and 7% include (in descending order) infection, headache, anemia, hypoproteinemia, asthenia, phlebitis, elevated blood urea nitrogen (BUN), abnormal healing, dizziness, skin rash, pneumonia, and abscess formation.[253]

Increased Mortality

In 2010 the FDA issued a warning of an increased risk of death with tigecycline compared with other antibiotics used to treat similar infections on the basis of pooled analysis of 13 clinical trials.[245] In those studies, death occurred in 4% (150/3788) of patients receiving tigecycline and 3% (110/3646) of patients receiving comparator drugs. Based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% confidence interval, 0.1–1.2) between tigecycline- and comparator-treated patients. Deaths were generally the result of worsening infection, complications of infections, or underlying comorbidities. Among indications, the mortality difference was not statistically significant. However, mortality in tigecycline-treated patients was numerically greater in every infection and considerably greater in VAP (19.1% vs. 12.3%). Study-level and patient-level analyses have identified that patients in the HAP trial, particularly those with VAP with baseline bacteremia, were at a higher risk of clinical failure and mortality.[247]

In 2013 the FDA approved a new boxed warning about this risk of death and warned health care professionals to reserve tigecycline for use in situations in which alternative treatments are not suitable. After the 2010 warning was issued, data were analyzed from 10 clinical trials conducted only for FDA-approved uses (cSSSI, cIAI, community-acquired bacterial pneumonia), including trials conducted after the drug was approved. This analysis showed a higher risk of death among patients receiving tigecycline compared with other antibacterial drugs: 2.5% (66/2640) versus 1.8% (48/2628), respectively. The adjusted risk difference for death was 0.6% with corresponding 95% confidence interval (0.0–1.2).[246]

Several meta-analyses prompted the FDA to look into the efficacy and safety of tigecycline. Depending on what clinical trials (published and unpublished) were included, results varied.[337–339]

Drug Interactions

In vitro studies in human liver microsomes have indicated that tigecycline is not a substrate, inhibitor, or inducer of common cytochrome P450 enzymes; therefore such pharmacokinetic drug interactions are unlikely.[340] However, concomitant administration of tigecycline and warfarin in healthy participants resulted in a decrease in clearance of *R*-warfarin and *S*-warfarin by 40% and 23%, an increase in C_{max} by 38% and 43%, and an increase in AUC by 68% and 29%, respectively.[253] No significant effects of tigecycline on digoxin pharmacokinetics and pharmacodynamics were noted in a study of 20 healthy men.[341]

NEW DRUG APPROVALS: ERAVACYCLINE AND OMADACYCLINE

Two new tetracycline derivatives were approved by the FDA in late 2018. Eravacycline is a fluorocycline antibiotic and is FDA approved for complicated intraabdominal infections in adults.[341a] Omadacycline is an aminomethylcycline and is FDA approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).[341b] Both drugs carry the same package insert label, which is to recommend that these two drugs should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. This precaution is to reduce the development of drug-resistant bacteria and maintain the effectiveness of eravacycline and omadacycline and other antibacterial drugs.[341c] Eravacycline also has a label precaution that it is not indicated for the treatment of complicated urinary tract infections. Omadacycline has an additional label precaution about the mortality imbalance in patients with CABP. In the CABP trial, a mortality rate of 2.1% was observed in omadacycline-treated patients compared to 0.8% in moxifloxacin-treated patients ($P = .14$).[341b] The cause of the mortality imbalance has not been established. Providers should closely monitor clinical response to therapy in CABP patients, particularly in those at higher risk for mortality.

Both drugs have broad in vitro activity against many gram-positive, gram-negative, atypical, and anaerobic bacteria, including activity against MRSA, VRE, penicillin-resistant *Streptococcus pneumoniae*, *A. baumannii*, and Enterobacteriaceae expressing extended-spectrum β-lactamases. Similar to tigecycline, neither agent performs well against *Pseudomonas* spp.

Eravacycline recommend dosing is 1 mg/kg by intravenous infusion every 12 hours. No dose adjustment is required in patients with renal impairment. In patients with severe hepatic impairment (Child Pugh C), the dose should be reduced starting on day 2 to 1 mg/kg every 24 hours. With concomitant use of a strong CYP3A inducer, the dose should be increased to 1.5 mg/kg every 12 hours. Omadacycline recommended dosing for ABSSSI and CABP is 200 mg by intravenous infusion on day 1 (given once or divided into two 100-mg doses), followed by 100 mg intravenously daily or 300 mg orally daily. For ABSSSI treatment, loading doses can be done with 450 mg orally once daily on days 1 and 2, followed by 300 mg orally daily. No dose adjustment is recommended in patients with renal or hepatic impairment. Both drugs have similar label warnings for patients who are on anticoagulant therapy that they may require downward adjustments of anticoagulant dosing while on these agents. Breastfeeding is not recommended while on either agent. Both drugs carry warning labels for permanent tooth discoloration and enamel hypoplasia, and reversible inhibition of bone growth if used during the second and third trimesters of pregnancy and during childhood up to age 8. Similar to other tetracyclines, omadacycline absorption is impaired by antacids containing aluminum, calcium, or magnesium; bismuth subsalicylate; and iron containing preparations.

CHLORAMPHENICOL

Chloramphenicol is a broad-spectrum antibiotic that has been in clinical use since 1949. It was developed from the soil organism *Streptomyces venezuelae*.[342] It remains an inexpensive drug that is active against many gram-positive, gram-negative, anaerobic, and atypical organisms. Because of the risk of aplastic anemia, chloramphenicol is no longer the drug of choice for any specific infection.[343,344] Its use in the developed world is limited to life-threatening infections without safer alternatives. However, it is still commonly used in many parts of the developing world.

Structure and Mechanism of Action

The structure of chloramphenicol is shown in Fig. 26.2. It has a paranitrobenzene ring attached to a propanediol group with a dichloracetamide side chain. Thiamphenicol, which is an analogue of chloramphenicol, is available in Europe and Japan, but not in the United States.

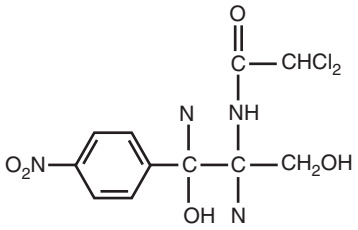

FIG. 26.2 **Chemical structure of chloramphenicol.**

Chloramphenicol inhibits protein synthesis by reversibly binding to the peptidyl transferase cavity of the 50S subunit of the bacterial 70S ribosome. This prevents the aminoacyl-tRNA from binding to the ribosome, thus terminating polypeptide chain synthesis.[345,346] Once chloramphenicol is removed, protein synthesis is able to resume if drug exposure was brief enough.[347] This mechanism results in bacteriostatic activity against most organisms. However, chloramphenicol is bactericidal at clinically achievable concentrations against some meningeal organisms such as *S. pneumoniae, N. meningitidis,* and *H. influenzae*.[348] It has been postulated that the dose-related bone marrow suppression of chloramphenicol is caused by its inhibition of protein synthesis in mammalian mitochondria, which contain 70S ribosomes.[349]

Pharmacology

Administration and Dosage

Chloramphenicol is available in multiple formulations. Oral preparations are 250-mg capsules and a 150-mg/mL palmitate solution. In the United States the oral preparations have not been manufactured since 1991. Intravenous preparations come in 1-g vials of sodium succinate powder for reconstitution. Infusions in adults are generally administered over a period of 30 minutes. There is an otic topical formulation that is a 0.5% otic solution, which is not available in the United States. There are a few different ophthalmic preparations: 0.5% solution, 1% ointment, and 25 mg/vial powder for ophthalmic solution. Only the ointment is available in the United States.

The recommended dose for newborn infants younger than 2 weeks old is 25 mg/kg/day divided in 6-hour intervals. Full-term infants older than 2 weeks can receive 50 mg/kg/day divided in 6-hour intervals. In older children and adults, the dose is 50 mg/kg/day divided in 6-hour intervals. For severe infections, such as meningitis, doses up to 100 mg/kg/day in 6-hour intervals may be used. The maximum daily intake should not exceed 4 g total.[344] Routine monitoring of serum concentrations should be performed, particularly in newborns and those with hepatic dysfunction. Peak serum levels between 15 and 25 mg/L have been suggested for children.[350,351] Others have suggested 10 to 20 mg/L and that levels higher than 25 mg/L are associated with toxicity.[352] If the white blood cell count decreases below 2500/μL, discontinuation of the drug should strongly be considered.

In patients with impaired renal function, usual doses may be administered because active chloramphenicol does not accumulate in the serum.[13] Inactive chloramphenicol metabolites do accumulate in the serum, but this has not been associated with toxicity.[353] Increased clearance of chloramphenicol occurs during dialysis, but this may be important only in patients with hepatic dysfunction. It is recommended that the normal maintenance dose of the drug be administered after dialysis to avoid the possibility of increased clearance.[354] Peritoneal dialysis does not alter the half-life of active chloramphenicol; thus the dose does not need adjustment.[355] Limited data exist for dosing during continuous renal replacement therapy.

Total body clearance of chloramphenicol is reduced in patients with liver dysfunction because the drug is metabolized by the liver.[356] Serum levels should be monitored closely.

Absorption and Bioavailability

Oral chloramphenicol capsules are approximately 80% bioavailable as they are rapidly absorbed from the intestinal tract. Serum levels with the oral palmitate solution are lower than with the capsule form. The palmitate ester is biologically inactive and is absorbed after being hydrolyzed by pancreatic lipases in the upper intestinal tract to free chloramphenicol. Even so, the oral palmitate ester can achieve higher serum levels as compared with the intravenous succinate form.[353] The rate of hydrolysis of the succinate by hepatic enzymes determines the concentration of active chloramphenicol, which is why oral preparations can be more bioavailable. Approximately 44% to 60% of the drug is bound to protein in the serum.[356] After a 1-g dose in adults, peak serum levels occur after 2 hours, with levels of 10 to 13 mg/L.[357] The half-life is 1.6 to 3.3 hours, and therapeutic levels may persist 6 to 8 hours after administration.[358]

Chloramphenicol succinate given intravenously has a wide variability of half-lives in infants. In adults, the serum half-life is approximately 1.2 hours, with an elimination half-life of approximately 4 hours.[353] Intramuscular injection is not recommended owing to variable hydrolysis and/or delayed absorption, leading to unpredictable serum concentrations.[359]

Drug Distribution

Chloramphenicol is highly lipid soluble and has good penetration into many body tissues, penetrates well into pleural and ascitic fluids, and also crosses the placenta and can be found in breast milk. It does not usually achieve adequate concentrations in the bile.[344] In bacterial peritonitis, drug levels in ascitic fluid can exceed half of the serum concentration.[360] Chloramphenicol is also able to achieve high levels in synovial fluid.[361] Even without inflamed meninges, chloramphenicol readily crosses the blood-brain barrier. CSF concentration may be 50% or more of the serum concentration, a higher proportion than with any other antibiotic.[362] Also, unlike most antibiotics, chloramphenicol can penetrate well into many parts of the eye.[363] It has also been shown to be concentrated in alveolar macrophages and polymorphonuclear leukocytes.[364]

Drug Elimination

Chloramphenicol is primarily metabolized by the liver, where it undergoes conjugation with glucuronic acid. The major metabolite is the inactive chloramphenicol glucuronide. This, along with other minor metabolites, is then eliminated through the urine (accounting for about 75%–90% of drug elimination). About 5% to 15% of the unchanged, active drug is eliminated through glomerular filtration. Less than 3% is eliminated through bile. Less than 1% is eliminated in feces.[358]

Antimicrobial Activity

Chloramphenicol has a broad spectrum of activity against many gram-positive and gram-negative bacteria, anaerobes, rickettsiae, chlamydiae, and mycoplasmas. As stated previously, chloramphenicol is generally bacteriostatic but may be bactericidal against meningeal organisms, especially at higher concentrations. For most organisms, susceptibility is defined as having an MIC value of 8 mg/L or less. Exceptions are *S. pneumoniae* (≤4 mg/L) and *H. influenzae* (≤2 mg/L).[365]

Gram-Positive Bacteria

Chloramphenicol has in vitro activity against streptococci, staphylococci, and enterococci. Resistance varies in many different geographic regions. In surveillance studies from the late 1990s, *S. pneumoniae* had higher rates of resistance in the Western Pacific Region and South Africa (17.1%), compared with Europe (12.7%), the United States (10.6%), Canada (4.5%), and Latin America (4.3%).[366,367] Chloramphenicol resistance is typically higher among penicillin-intermediate and penicillin-resistant strains.

In a North American surveillance study, chloramphenicol had activity against 81.6% of all *S. aureus* isolates tested.[368] Another North American study also reported high susceptibility rates to both methicillin-sensitive (96%) and methicillin-resistant (81%) strains.[369] Chloramphenicol has also been demonstrated to have activity against vancomycin-intermediate and vancomycin-resistant strains.[370,371]

Against *Enterococcus* spp., chloramphenicol susceptibility rates in North America have been shown to be 87%.[372] In another study of 886 VRE isolates, investigators reported that 28.6% of 56 *E. faecalis* isolates from North America were chloramphenicol resistant, compared with 7.1% of 14 isolates from Europe. This was in contrast to *E. faecium* isolates. In North America, 0.5% of 776 isolates were resistant, compared with 15% of 40 isolates from Europe, the latter a result of clonal occurrences.[373]