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## Preface

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Antibiotics have cured countless diseases and have saved countless lives. The stellar success of these “wonder drugs” over the past six decades has led to their widespread use (see accompanying table) and this, in turn, has driven the development of many therapeutic options. As our options increase, however, so does the complexity of therapeutic decisions and the risks associated with antibiotic use. The risks to individual patients include life-threatening adverse reactions, treatment failures due to errors in choice of therapy, and treatment failures due to antimicrobial resistance. The risk to institutions and entire populations is the development of organisms that are resistant to all available agents. An understanding of antimicrobial pharmacology is necessary to minimize these risks, and it is for this reason that antimicrobial pharmacology is a critical component of the medical school curriculum.

This guide is derived from the lecture notes prepared for second year medical students at the University of Pennsylvania School of Medicine. These notes have evolved through the efforts of both faculty and students to gauge what *can* be assimilated in the midst of an overwhelming amount of other material, and what *must* be assimilated about this subject to understand the general literature of medicine. If we have been successful, then this text contains the information that is essential for medical students to know at the conclusion of their pre-clinical studies, as well as the information that practicing physicians must know to remain up-to-date. Pharmacists, nurses, and even business analysts should also find that this is the information they need to understand new developments in the field.

In keeping with its intended role as a “guide” (rather than a textbook for a first-time introduction to the subject), the text is intentionally succinct in style and format. It is a secondary tool that will be most effectively used as a reference, as a review aid, or—as used at Penn—in conjunction with a didactic lecture series. The tables and figures (including figure captions and chemical structures) are provided only to assist in assimilating the text; they should not be regarded as essential to an understanding of the subject.

The author thanks the many expert friends and wise colleagues who offered advice or encouragement in the course of developing lec-

ture notes, and at various stages of text preparation: P.J. Brennan, Helen Davies, Paul Edelstein, Neil Fishman, Ian Frank, Harvey Friedman, Al Goldin, Marilyn Hess, Rob Roy MacGregor, Greg Poland, David Relman, Harvey Rubin, Mindy Shuster, Jeff Weiser, and students in the Pharmacology Graduate Group at the University of Pennsylvania.

As an initial attempt to define an essential body of knowledge about antibiotic pharmacology, the contents of this volume are subject to revision. Suggestions for inclusion or omission are welcome.

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*Note: Most information about currently marketed antibiotics presented in the tables is derived from the National Drug Code Directory updated on March 31, 2001 by the United States Food and Drug Administration. Readers are referred to <http://www.fda.gov> for more recent updates.*

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**Antibiotics Among the 200 Most Commonly  
Prescribed Medications in 1999 (From [www.rxlist.com](http://www.rxlist.com))**

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<i>Rank</i>	<i>Generic Name</i>	<i>Trade Name</i>
9	Amoxicillin	Trimox
16	Azithromycin	Zithromax (Z-Pack)
20	Amoxicillin/Clavulanate	Augmentin
25	Amoxicillin	(generic)
28	Ciprofloxacin	Cipro
29	Cephalexin	(generic, manufacturer #1)
33	Amoxicillin	Amoxil
34	Trimethoprim/Sulfamethoxazole	(generic)
35	Clarithromycin	Biaxin
51	Azithromycin	Zithromax
69	Fluconazole	Diflucan
79	Levofloxacin	Levaquin
82	Cefprozil	Cefzil
98	Penicillin VK	Veetids
102	Cefuroxime	Ceftin
107	Clotrimazole/Betamethasone	Lotrisone
131	Mupirocin	Bactroban
135	Amoxicillin	(generic)
145	Penicillin VK	(generic)
146	Neomycin/Polymyxin/Hydrocortisone	Neomycin/Polymyxin/Hydrocortione
152	Cephalexin	(generic, manufacturer #2)
158	Erythromycin	Ery-Tab
184	Tobramycin/Dexamethasone	Tobradex
188	Terbinafine	Lamisil

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## 2 Antibacterial Agents

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### 2.1 Cell Wall Active Agents (Table 2.1.1)

Bacterial cell walls in both Gram-positive and Gram-negative bacteria contain peptidoglycan. Peptidoglycan precursors are synthesized intracellularly and attached to carrier molecules for export from the cell. Following export from the cell, specific enzymes catalyze transglycosylation reactions in which the peptidoglycan precursors are transferred from their carrier molecules to existing polyglycan chains. Once transferred, other specific enzymes catalyze transpeptidation reactions in which two polypeptide segments are joined. In this manner, a densely crosslinked molecular mesh is created.

The specific chemical composition of peptidoglycan can vary widely between different bacterial species, but it tends to be chemically homogeneous within any one species. Compounds that inhibit individual enzymes involved in peptidoglycan synthesis, or mutations that render individual enzymes inactive give rise to morphologically distorted bacterial cells. This demonstrates the role of peptidoglycan in maintaining bacterial shape. In addition to enzymes that synthesize peptidoglycan, bacteria produce lytic enzymes that remove the crosslinks formed during transpeptidation. Complexes composed of lytic and synthetic enzymes enable bacteria to sever and reform crosslinks in such a way as to permit growth while preserving cell wall integrity (Fig. 2.1.1).

**Table 2.1.1**  
**Currently Marketed Bacterial Cell Wall Biosynthesis Inhibitors**

Subclass	Generic name	O	IV	IM	T	Trade names
Natural penicillins	Penicillin G	X	X	X	X	Penicillin, <sup>a</sup> Truxcillin, Pfizerpen
	Penicillin G benzathine			X		Bicillin L-A, Bicillin C-R <sup>a</sup> Permapen
	Penicillin G procaine			X		Wycillin, Bicillin C-R <sup>a</sup>
	Penicillin V	X				Pen, Penicillin <sup>a</sup> , V-Cillin, Veetids, Penicillin-Vk, Beepen, Peniclin, Truxcillin-Vk
Aminopenicillins	Ampicillin	X	X	X		Unasyn, <sup>a</sup> Principen, Amficot, <sup>a</sup> Omnipen
	Amoxicillin	X				Amoxil, Amoxycillin, Amficot, <sup>a</sup> Moxilin, Amoxocillin, Amoxicot, Augmentin, <sup>a</sup> Trimox, Sumox
Antistaphylococcal (β-lactamase-resistant) penicillins	Bacampicillin			X		Spectrobid
	Nafcillin		X		X	Nalpen
	Oxacillin	X	X	X		Bactocill
	Dicloxacillin	X				Dycill, Dynapen
Broad-spectrum antipseudomonal penicillins	Carbenicillin		X			Geocillin
	Mezlocillin		X	X		Mezlin
	Piperacillin		X	X		Zosyn, <sup>a</sup> Pipracil
	Ticarcillin		X	X		Ticar, Timentin <sup>a</sup>
First-generation cephalosporins	Cefadroxil	X				Duricef
	Cefazolin		X	X		Kefzol, Ancef
	Cephalexin	X				Keftabs, Keftab, Keflex, Biocef
	Cephapirin		X	X		Cefadyl
Cephradine	X				Velosef	

Second-generation cephalosporins	Cefaclor	X				Ceclor
	Cefamandole		X			Mandol
	Cefmetazole		X			Zefazone
	Cefonicid		X			Monocid
	Cefotetan		X			Cefotan
	Cefoxitin		X			Mefoxin
	Cefprozil	X				Cefzil
	Cefuroxime		X			Kefurox, Zinacef
	Cefuroxime axetil	X			X	Ceftin
	Loracarbef	X				Lorabid
	Cefdinir	X				Omnicef
	Cefixime	X				Suprax
	Cefoperazone		X		X	Cefobid
	Cefotaxime		X		X	Claforan
Cefpodoxime proxetil	X				Vantin	
Ceftazidime		X		X	Ceptaz, Tazidime, Tazicef, Fortaz	
Ceftibuten	X				Cedax	
Ceftizoxime		X		X	Cefizox	
Ceftriaxone		X		X	Rocephin	
Cefepime		X		X	Maxipime	
Fourth-generation cephalosporins						
Carbapenams	Imipenem		X			Primaxin <sup>a</sup>
	Meropenam		X			Merrem
Monobactams	Aztreonam		X			Azactam
Glycopeptides	Vancomycin	X				Vancoled, Vancocin

<sup>a</sup>Multicomponent product

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears

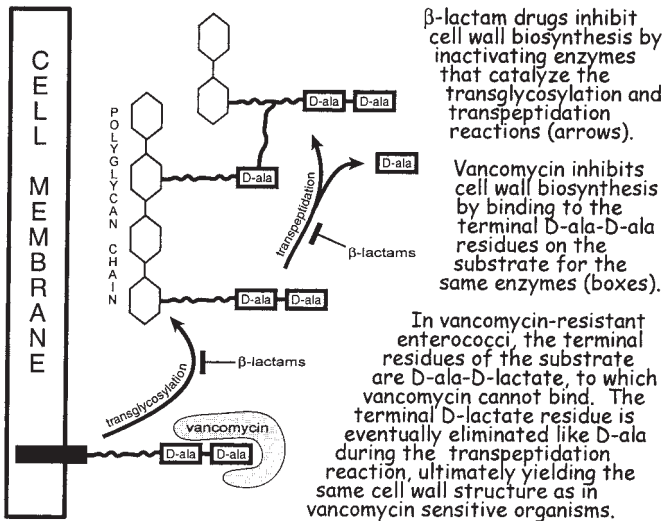
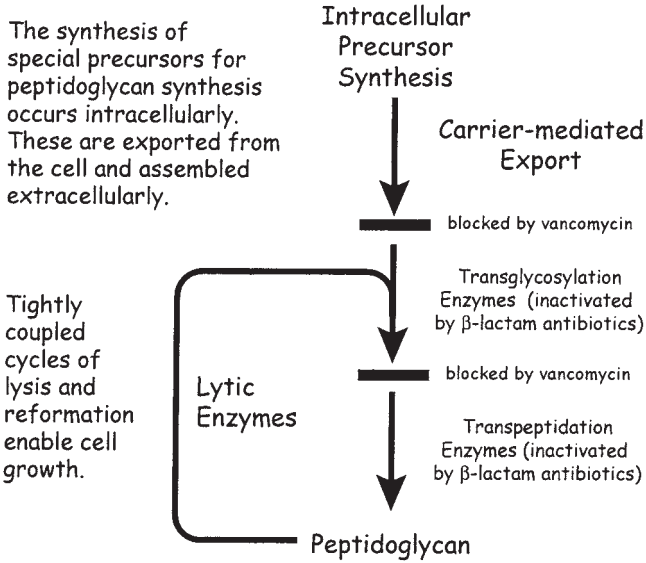


Fig. 2.1.1



**BETA LACTAMS***Identity*

All antibiotics in this class possess a  $\beta$ -lactam ring (**Fig. 2.1.2**). A “lactam” is an amide (a C=O group adjacent to an NH group) within a ring. The prefix  $\beta$  indicates that the ring is comprised of four atoms. Different  $\beta$ -lactam subclasses differ in the kind of ring fused with the  $\beta$ -lactam ring. Different groups attached to these rings distinguish individual drugs within each subclass, altering the pharmacokinetic properties and antimicrobial activity of the parent compound.

*Mechanism of Action*

$\beta$ -Lactams are unstable compounds with chemically strained four-atom rings that become more stable when the ring is opened by cleavage of the CO–NH bond. When this occurs, the open ring form typically binds to proteins via its C=O group. This reaction is called “acylation,” and it may be compared to the release of tension in a safety pin upon opening.  $\beta$ -Lactam antibiotics specifically and permanently acylate the active site of the enzymes that catalyze the transglycosylation and transpeptidation reactions involved in peptidoglycan synthesis. Collectively, these enzymes are known as penicillin binding proteins, or PBPs. The lethal event is probably the continued activity of lytic enzymes (**Fig. 2.1.1**) that are not inhibited by  $\beta$ -lactam compounds, and the consequent loss of cell wall integrity.

*Activity*

One might expect that any bacterium with a peptidoglycan cell wall would be susceptible to the action of  $\beta$ -lactam drugs. However, differences among bacteria in the types of enzymes used to synthesize peptidoglycan and a variety of other factors result in wide variations in susceptibility to different drugs (**Table 2.1.2**).

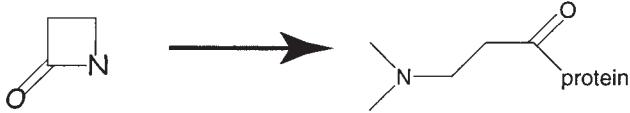
*Administration, Metabolism, and Elimination*

The bioavailability of  $\beta$ -lactam antibiotics is highly variable, and adequate blood levels cannot always be attained by oral administration. Due to active secretion by cells lining the proximal renal tubules, in addition to glomerular filtration, natural penicillins have serum half-lives as short as 30 min. Active secretion can be inhibited by concomitant administration of probenecid.

Imipenem (but not meropenem) is degraded by an enzyme in the proximal renal tubule into nephrotoxic products. For this reason,

All  $\beta$ -lactam antibiotics have a  $\beta$ -lactam ring . . .

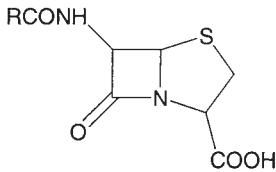
. . . and acylate the active sites of target enzymes.



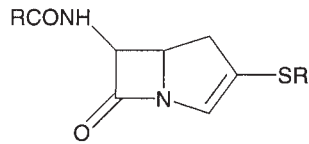
Opening of a  $\beta$ -lactam ring is associated with the release of bond-angle strain. The release of this strain may be compared to the release of energy that occurs when a safety pin is opened.



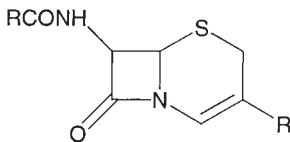
Major subclasses differ in the type of ring adjacent to the  $\beta$ -lactam ring, and different "R" groups distinguish different drugs within a subclass. R groups determine the pharmacokinetics and metabolism of a drug, as well as its spectrum of antimicrobial activity.



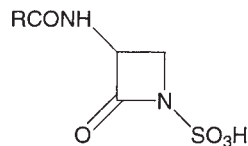
Penicillins



Carbapenams



Cephalosporins



Monobactams

Fig. 2.1.2

it is administered concomitantly with an inhibitor of this enzyme, cilastatin. All  $\beta$ -lactams are primarily eliminated unchanged into the urine *except* drugs in the antistaphylococcal class (metabolized in the liver), and two of the third-generation cephalosporins (cefoperzone and ceftriaxone are eliminated unchanged into the bile).

#### *Adverse Effects*

***Hypersensitivity.*** The overall incidence of hypersensitivity reactions is roughly 10% in patients treated with any  $\beta$ -lactam agent. Most of these reactions are mild maculopapular exanthems (skin rash), sometimes accompanied by urticaria, fever, and/or eosinophilia. Other types of hypersensitivity reactions also occur including hemolytic anemia and serum sickness. Fatal anaphylaxis and/or angioedema occur in  $\sim 1/100,000$  patients treated with any  $\beta$ -lactam agent.

The most important antigenic forms are not  $\beta$ -lactams, but opening derivatives that have nonspecifically acylated tissue proteins. Thus,  $\beta$ -lactams sensitize the immune system by functioning as antigenic haptens.

Hypersensitivity to one  $\beta$ -lactam agent implies a relatively higher likelihood of a hypersensitive cross-reaction to another  $\beta$ -lactam agent. Between penicillins and cephalosporins, the incidence of cross-reacting hypersensitivity reactions has been estimated to be 10%. Between either of these classes and the carbapenems, the incidence is believed to be higher; between these classes and the monobactams, the incidence appears to be substantially lower.

The incidence of exanthem when administering ampicillin/amoxicillin to patients with Epstein–Barr virus infections (e.g., infectious mononucleosis) approaches 100%. The mechanism of this is not known, but it is not a true hypersensitivity reaction and it is no contraindication to future treatment with any  $\beta$ -lactam agent.

***Jarish–Herxheimer Reaction.*** Severe reactions resembling anaphylactic shock may occur following the administration of  $\beta$ -lactam agents to persons with syphilis. Classically, the reaction occurs within 2 h of treating secondary syphilis with penicillin, but it may occur in other stages of syphilis, with other spirochetal infections (e.g., Lyme), and with agents other than  $\beta$ -lactams. The reaction is due to the release of pyrogens from killed spirochetes, and is not a contraindication to future treatment with the same agent.

**Table 2.1.2**  
 **$\beta$ -Lactam Antibiotic Subclasses**

<b>Class (examples)</b>	<b>Activity</b>	<b>Comments</b>
<b>Natural penicillin (PCN)</b> (penicillin G, penicillin V)	Streptococci, enterococci, Gram-negative cocci and some bacilli, spirochetes	Despite their introduction six decades ago, these remain the drugs of choice for serious infections (e.g., sepsis, meningitis, pneumonia) caused by susceptible organisms
<b>Aminopenicillins</b> (ampicillin, amoxicillin)	As for PCN, but with broader activity against Gram-negative bacilli	Widely used for otitis, sinusitis, and urinary tract infections
<b>Antistaphylococcal or <math>\beta</math>-lactamase resistant penicillins</b> (methicillin, nafcillin, oxacillin)	Staphylococcus aureus	Effective against $\beta$ -lactamase producing bacterial strains, but <i>not</i> against methicillin- resistant <i>S. aureus</i> (MRSA)
<b>Broad-spectrum or antipseudomonal penicillins</b> (piperacillin, mezlocillin, ticarcillin)	Broad activity against Gram-negative bacilli including pseudomonas, also many anaerobic species and enterococci	Used for infections due to pseudomonas and gastrointestinal flora, and for sepsis in immunocompromised hosts
<b>First-generation cephalosporins</b> (cefazolin, cephalexin)	Staphylococcus and Streptococcus species, some Gram-negative bacteria but not enterococci or gastrointestinal anaerobes	Effective against $\beta$ -lactamase producing bacterial strains, but not MRSA. Widely used for prophylaxis in surgery.
<b>Second-generation cephalosporins</b> (cefotixin, cefuroxime, cefotetan)	Compared to first-generation cephalosporins, more Gram-negative activity, less Gram-positive activity, some activity against anaerobic species	Narrow therapeutic niche; prophylaxis in some types of surgical procedures, treatment of pelvic inflammatory disease, mixed aerobic/ anaerobe infections

<p><b>Third-generation cephalosporins</b> (ceftriaxone, cefotaxime, ceftazidime, ceftizoxime, cefoperazone)</p>	<p>Broad Gram-negative activity including pseudomonas; little Gram-positive activity</p>	<p>Sometimes the only good therapeutic option for infections due to Gram-negative species; useful for some common sexually transmitted infections (<i>N. gonorrhoea</i>, <i>T. pallidum</i>) and Lyme disease. The only cephalosporin class that reliably penetrates the blood–brain barrier.</p>
<p><b>Fourth-generation cephalosporins</b> (cefepime)</p>	<p>More Gram-positive activity than third-generation cephalosporins</p>	<p>Appears to evade destruction by <math>\beta</math>-lactamases in Gram-negative bacteria by rapidly traversing the periplasm</p>
<p><b>Monobactams</b> (aztreonam)</p>	<p>Broad Gram-negative activity including pseudomonas; little Gram-positive activity</p>	<p>Least likely <math>\beta</math>-lactam agent to trigger hypersensitivity reaction in a patient that is hypersensitive to other <math>\beta</math>-lactams</p>
<p><b>Carbapenems</b> (imipenem, meropenem)</p>	<p>Broadest Gram-negative and Gram-positive activity of any <math>\beta</math>-lactam class</p>	<p>Not effective against MRSA, <i>Xanthomonas</i> species, or enterococci</p>

**Interstitial Nephritis.** Impaired renal function with fever, proteinuria, and hematuria is most commonly associated with methicillin, but it can occur with  $\beta$ -lactams from any class.

**Platelet Dysfunction.** Moxalactam and cefoperazone are associated with platelet dysfunction and bleeding due to the presence of methylthiotetrazole groups.

#### *Drug Interactions*

Uncommon.

#### *Mechanisms of Resistance*

**$\beta$ -Lactamase Production.**  $\beta$ -Lactamase production is the most common mechanism of resistance to  $\beta$ -lactam antibiotics.  $\beta$ -Lactam drugs acylate the active sites of a  $\beta$ -lactamase enzyme in the same way that they acylate the penicillin binding proteins that synthesize the cell wall. However, the acylation of penicillin binding proteins is permanent, while the acylation of a  $\beta$ -lactamase is transient: the enzyme releases the drug as an inactive open-ring form. The net result of this encounter is the destruction of active drug, while enzyme activity is retained.

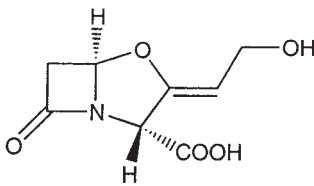
Many kinds of  $\beta$ -lactamases are known, some with broad nonspecific activity, and some with very specific activity (e.g., oxacillinase, carbenicillinase). They may be chromosomally or plasmid encoded, and constitutively or inducibly expressed. A latent (inducible) capacity to produce  $\beta$ -lactamase can account for the failure of therapy with  $\beta$ -lactam agents when the infecting organism initially appears susceptible.

Gram-positive organisms produce relatively large amounts of  $\beta$ -lactamase because they must secrete the enzyme into an open environment and it must be present in high enough concentration to destroy approaching drug molecules. Gram-negative organisms produce relatively small amounts of  $\beta$ -lactamase because after it is secreted it remains sequestered in the periplasmic space.

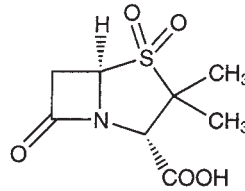
Chemical agents are available that specifically inhibit some  $\beta$ -lactamases (e.g. clavulanic acid, sulbactam, and tazobactam. **Fig. 2.1.3.** These agents are  $\beta$ -lactams, but they are not effective as antibiotics. They bind permanently to  $\beta$ -lactamases, and are not released as open ring forms (they exclude water from their binding site; water is necessary to hydrolyze the acyl group and release the open ring form). Treatment with a  $\beta$ -lactamase inhibitor can overcome resistance

## $\beta$ -lactam drugs and $\beta$ -lactamases

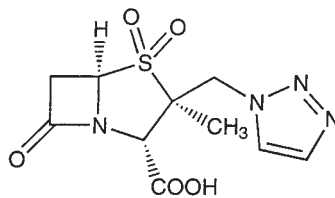
Interaction with a $\beta$ -lactamase	Drug	Interaction with a penicillin binding protein
Transient	$\beta$ -lactamase susceptible $\beta$ -lactam antibiotic	Permanent
None	$\beta$ -lactamase resistant $\beta$ -lactam antibiotic	Permanent
Permanent	$\beta$ -lactamase inhibitor	None



clavulanic acid



sulbactam



tazobactam

Fig. 2.1.3

due to the production of certain types of  $\beta$ -lactamase.  $\beta$ -Lactamase inhibitors are only available in combination with a  $\beta$ -lactamase susceptible agent (amoxicillin and clavulanate—Augmentin; ampicillin and sulbactam—Unasyn; ticarcillin and clavulanate—Timentin; piperacillin and tazobactam—Zosyn).

**Porin Deficiency.** Porins are specialized channel-forming proteins in the outer membrane of Gram-negative organisms.  $\beta$ -Lactam compounds must penetrate the outer membrane of Gram-negative bacteria to reach their site of action, and the channels formed by porins are necessary in some cases for penetration. Thus, porin deficiency can account for resistance to the action of certain  $\beta$ -lactam agents, most notably cephalosporins and carbapenems.

**Methicillin Resistance.** Methicillin resistance is due to a mutated form of a penicillin binding protein that results in a low affinity for all  $\beta$ -lactam compounds. Methicillin resistance implies resistance to all  $\beta$ -lactam antibiotics.

**Autolysin Deficiency.** A deficiency of lytic enzymes gives rise to a “penicillin tolerant” phenotype. Although these organisms may not have the virulence of wild-type organisms, the lack of autolytic enzymes can make the eradication of an infection more difficult.

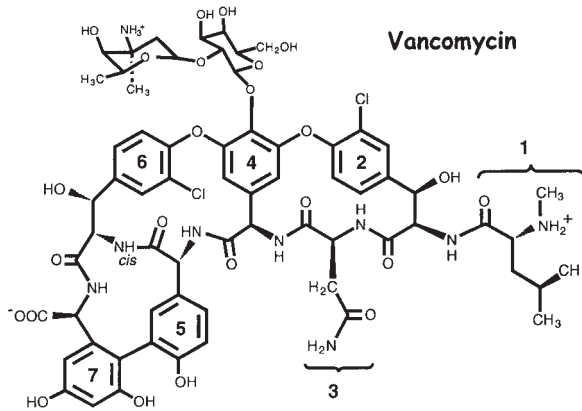
## GLYCOPEPTIDES

### *Identity*

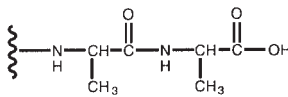
Glycopeptide antibiotics are chemically complex compounds produced by bacteria and purified for therapeutic use (**Fig. 2.1.4**). They cannot be produced synthetically. They are called glycopeptides because they contain sugar and amino acid residues. Most of the amino acids are not among the 20 amino acids found in proteins, implying that vancomycin is not produced by the translation of a genetic sequence.

More than 100 glycopeptide antibiotics have been identified in nature, but vancomycin is the only one licensed for use in the United States. Teicoplanin is used in Europe. It differs in several respects from vancomycin, most notably in having a lipophilic chain that presumably “anchors” the molecule in lipid membranes. Ristocetin caused bleeding in early trials, and has been deemed too toxic for therapeutic use. For reasons related to this side effect, however, it is

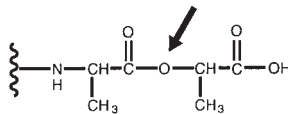




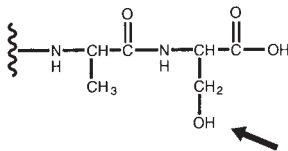
Vancomycin consists of a glucose-vancosamine disaccharide attached to a seven-residue polypeptide chain (residue side chains are numbered). Six of the seven amino acid residues are not among the 20 residues found in proteins, indicating that the polypeptide portion of vancomycin is not genetically encoded, nor is it synthesized on ribosomes.



The target of vancomycin action is D-alanyl-D-alanine dipeptide, an intermediate in the synthesis of cell wall peptidoglycan in susceptible bacteria.



Vancomycin-resistant enterococci (*vanA* and *VanB* phenotypes) have replaced D-alanyl-D-alanine with D-alanyl-D-lactate, to which vancomycin cannot bind.



Other vancomycin-resistant bacteria have replaced D-alanyl-D-alanine with D-alanyl-D-serine, to which vancomycin also cannot bind.

Fig. 2.1.4

now used in clinical laboratories for the diagnosis of von Willebrand's disease.

#### *Mechanism of Action*

In vancomycin-susceptible organisms, there are two D-alanine residues at the C-terminus of the peptidoglycan precursor prior to crosslinking in the transpeptidation step of peptidoglycan synthesis. During transpeptidation, the terminal D-alanine residue is lost, and the penultimate D-alanine residue is linked to another peptidoglycan precursor. Vancomycin specifically recognizes and binds to the D-alanyl-D-alanine dipeptide, preventing the transpeptidation reaction (**Fig. 2.1.1**).

Transpeptidation enzymes bind  $\beta$ -lactam antibiotics because  $\beta$ -lactam antibiotics are molecular mimics of the D-alanyl-D-alanine dipeptide. As might be expected, therefore, vancomycin has some affinity for  $\beta$ -lactam antibiotics, although its affinity is too low to cause any significant drug–drug interaction.

#### *Activity*

Glycopeptide antibiotics are active only against Gram-positive organisms whose peptidoglycan precursors have terminal D-alanyl-D-alanine dipeptides. Vancomycin is excluded from its site of action by the outer membrane of Gram-negative bacteria, and the peptidoglycan precursors of some pathologically significant Gram-positive bacteria terminate with D-alanyl-D-serine dipeptides or D-alanyl-D-lactate depsipeptides that are not recognized by vancomycin (**Fig. 2.1.4**). Vancomycin is commonly used against staphylococci, streptococci, and enterococci when attempting to overcome resistance or circumvent hypersensitivity reactions to other agents.

#### *Administration, Metabolism, and Elimination*

Vancomycin is administered orally only in the treatment of antibiotic-induced colitis because it is not absorbed from the gastrointestinal tract. In all other cases, it is administered intravenously. It is eliminated unchanged in the urine.

Compared to most other antibiotics, vancomycin has a narrow therapeutic index. This necessitates diligent pharmacokinetic monitoring of blood levels during therapy. Although vancomycin is relatively inexpensive, the costs of intravenous administration and monitoring make the cost of vancomycin therapy relatively high.

*Adverse Effects*

Auditory nerve damage with tinnitus, dysequilibrium, and hearing loss is common with higher blood levels. This damage is particularly serious because it is usually irreversible.

Early impure preparations were associated with nephrotoxicity, but this is not a significant problem with current preparations.

Rapid intravenous infusion can cause thrombophlebitis and/or the “red man syndrome” with facial flushing, hypotension, and shock due to the stimulation of histamine release. The symptoms resolve quickly when the infusion is halted, and usually do not recur if the infusion is resumed at a slower rate. Thus, it is not a hypersensitivity reaction, and is not a contraindication to further therapy with vancomycin.

*Drug Interactions*

None of clinical significance.

*Mechanisms of Resistance*

There are at least two explanations for the slow emergence of vancomycin resistance. First, it binds to the substrate of the transglycosylation/transpeptidation reactions, rather than to the enzymes catalyzing these reactions. Because this substrate is the result of a complex multicomponent biosynthetic pathway, it is unlikely that resistance could arise from a simple single-site mutation. Second, vancomycin must be administered intravenously. This relegated it to relatively infrequent use in hospitalized patients and reduced both the selective pressure for resistance and the likelihood of suboptimal dosing. Vancomycin was used for several decades under the assumption that staphylococci, streptococci, and enterococci were uniformly susceptible. Since 1989, however, enterococci are being isolated in increasing numbers with a plasmid-encoded set of enzymes that provide for peptidoglycan synthesis by an inducible alternative path (**Fig 2.1.4**). When both vancomycin and teicoplanin induce this path, the resistance phenotype is designated vanA. When vancomycin but not teicoplanin induces this path, the phenotype is designated vanB. Other less common inducible resistance phenotypes also exist, as does constitutive resistance (e.g., *Lactobacillus spp.*).

It is likely that the heavy use of avoparcin, a closely related glycopeptide antibiotic, as a growth promoting additive to animal feed in Europe was a major factor in the emergence of vancomycin resistance.

The incidence of vancomycin-resistant enterococci now exceeds 50% of all enterococcal infections in many hospitals, making this a major public health problem.

Strains of methicillin-resistant *S. aureus* have been isolated that exhibit an intermediate level of susceptibility to vancomycin. Morphologically, these organisms exhibit exceptionally thick cell walls, and the clinical significance of this reduced susceptibility is not clear at this time.

## 2.2 Antifolate Agents (Table 2.2)

### *Identity*

Sulfonamides are simple synthetic compounds related to *p*-aminobenzoic acid (**Fig. 2.2**). Dapsone is so named because it is a symmetric di-anilino-para-sulfone. Trimethoprim and pyrimethamine do not contain sulfur.

### *Mechanism of Action*

Many bacteria absorb *p*-aminobenzoate, convert it into dihydrofolate and tetrahydrofolate, and then ultimately use it to synthesize purines for nucleic acid (**Fig. 2.2**). By virtue of their chemical resemblance to *p*-aminobenzoate, sulfonamides inhibit the synthesis of folates. In contrast, human metabolism relies on dietary folates, and some bacteria have developed means to absorb preformed folates in their environment. Thus, they are unaffected by the action of sulfonamides.

Trimethoprim and pyrimethamine inhibit the conversion of dihydrofolate to tetrahydrofolate by bacterial forms of dihydrofolate reductase. The human form of dihydrofolate reductase is relatively insensitive to inhibition by these drugs (although it is highly sensitive to inhibition by the anticancer agent methotrexate).

Sulfonamides and trimethoprim are commonly used in combination because (a) they inhibit two different reactions on the same metabolic pathway and thus exhibit synergistic activity, and (b) the combination reduces the likelihood that resistance will develop.

### *Activity*

Many organisms once susceptible are now resistant to sulfonamides, often due to single-step mutations in the target enzyme. However, useful activity still includes many Gram-positive and Gram-negative

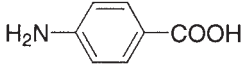
**Table 2.2**  
**Currently Marketed Antifolate Antibiotics**

Generic name	Oral	IV	IM	Top	Trade names	
Mafenide				X		Sulfamylon
Sulfabenzamide				X		Gyne-Sulf, <sup>a</sup> Triple-sulfa, <sup>a</sup> Trysul, <sup>a</sup> Sultrin, <sup>a</sup> Dayto <sup>a</sup>
Sulfacetamide				X		Al-Cide, Vasosulf, Vasocidin, Triple-sulfa, <sup>a</sup> Blephamide, Bleph-10, Dayto, <sup>a</sup> Cetaped, Trysul, <sup>a</sup> Bleph, Predsulfair, Sulf-10, Sulfac, Sulf, Metimyd, Fml, Fml-S, Klaron, Gyne-Sulf, <sup>a</sup> Ocusulf, Isopto, Sulster, Sultrin <sup>a</sup>
Sulfacytine	X					Renoquid
Sulfadiazine	X					Triple-sulfa <sup>a</sup>
Sulfadoxine	X					Fansidar <sup>a</sup>
Sulfamerazine	X					Triple-sulfa <sup>a</sup>
Sulfamethazine	X					Triple-sulfa <sup>a</sup>
Sulfamethizole	X					Urobiotic-250 <sup>a</sup>
Sulfamethoxazole	X	X				Bethaprim, <sup>a</sup> Bactrim, <sup>a</sup> Sulfameth/Trimeth, <sup>a</sup> Smz-Tmp, <sup>a</sup> Sulfameth, <sup>a</sup> Sulfamethoxazole, <sup>a</sup> Cotrim, <sup>a</sup> Sulfatrim, <sup>a</sup> Sultrex, <sup>a</sup> Gantanol, Septra, <sup>a</sup> Smx, <sup>a</sup> Bacter-Aid, <sup>a</sup> Trimeth, <sup>a</sup> Trimethoprim <sup>a</sup>
Sulfanilamide				X		Avc
Sulfasalazine	X					Azulfidine
Sulfathiazole	X			X		Dayto, <sup>a</sup> Gyne-Sulf, <sup>a</sup> Triple-sulfa, <sup>a</sup> Trysul, <sup>a</sup> Sultrin <sup>*</sup>
Sulfisoxazole	X					Eryzole, <sup>a</sup> E, Azo, <sup>a</sup> Ery, Pediazole, <sup>a</sup> Peditagen, <sup>a</sup> Erythro-Sul, <sup>a</sup> Truxazole, Gantrisin
Trimethoprim	X	X		X		Sulfameth, <sup>a</sup> Polytrim, <sup>a</sup> Sulfatrim, <sup>a</sup> Sulfamethoxazole, <sup>a</sup> Bactrim, <sup>a</sup> Proloprim, Smz, <sup>a</sup> Septra, <sup>a</sup> Smz-Tmp, <sup>a</sup> Bethaprim, <sup>a</sup> Sultrex, <sup>a</sup> Smx, <sup>a</sup> Bacter-Aid, <sup>a</sup> Sulfamethoxazole, Cotrim, <sup>a</sup> Trimeth, <sup>a</sup> Trimethoprim/, Trimex, Sulfameth/Trimeth <sup>a</sup>

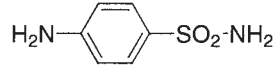
<sup>a</sup>Multicomponent product

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears

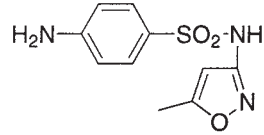
para-amino benzoic acid



Inhibited by  
sulfonamides  
and dapsone



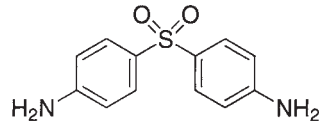
sulfanilamide



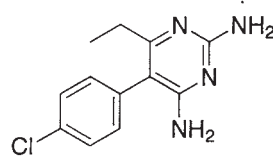
sulfamethoxazole

dihydrofolate  
(dietary folate)

dihydrofolate  
reductase,  
inhibited by  
trimethoprim  
and  
pyrimethamine

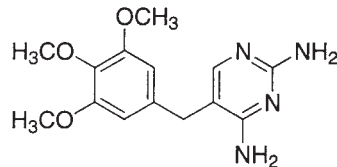


dapsone



pyrimethamine

tetrahydrofolate



trimethoprim

purine synthesis

Fig. 2.2

organisms as well as actinomyces, chlamydia, malaria, pneumocystis, and toxoplasma. Trimethoprim has been used as a single agent for the treatment of urinary tract infections and traveler's diarrhea, but is much more widely used in a fixed combination with sulfamethoxazole to achieve synergistic activity. Pyrimethamine is combined with sulfadoxine for use against chloroquine-resistant malaria, and with dapsone for use against pneumocystis. Dapsone also has an important role in the treatment of leprosy.

#### *Administration, Metabolism, and Elimination*

Most drugs in this class are well absorbed from the gastrointestinal tract and distribute well into most tissues including the central nervous system (CNS). Most are eliminated unchanged into the urine, although some undergo modification in the liver before elimination into the urine. The only significant exception is sulfasalazine, which is poorly absorbed from the gastrointestinal tract. This drug passes through to the colon where it is metabolized by bacterial enzymes into sulfapyridine and 5-amino-salicylic acid. The latter has local anti-inflammatory effects and most likely accounts for the beneficial effects of sulfasalazine in inflammatory bowel disease.

The rate at which sulfonamides are eliminated in the urine varies according to the extent to which they are protein bound. Short-acting sulfonamides with half-lives of <20 h are used primarily for urinary tract infections because their rapid elimination results in high urinary concentrations. Sulfamethoxazole is frequently combined with trimethoprim (cotrimoxazole) because they have similar and relatively slow rates of elimination. This helps maintain optimal relative concentrations in the blood. Sulfadoxine has a half life of 100–200 h, and can therefore be used for once-per-week dosing.

#### *Adverse Effect*

Hypersensitivity reactions are common. Most often these reactions are minor exanthems, but a variety of more severe reactions are all known to occur. Long-acting forms are associated with a severe life-threatening hypersensitivity reaction known as the Stevens–Johnson syndrome, particularly in children.

Sulfonamides can cause hemolysis in glucose 6-phosphate dehydrogenase (G6PD) deficient patients, and rapidly eliminated forms

can cause crystalluria. This is best avoided by maintaining alkaline urine and high output.

#### *Drug Interactions*

Sulfonamides displace many other drugs from plasma proteins, acutely raising their potency, but subacutely increasing their rate of elimination. These include warfarin, methotrexate, oral contraceptives, oral hypoglycemic agents, thiazide diuretics, and phenytoin. Sulfonamide kinetics may be altered when they are displaced from protein binding sites by common antiinflammatory drugs such as salicylates, indomethacin, and phenylbutazone.

#### *Mechanisms of Resistance*

Resistance to sulfonamides and trimethoprim is widespread and operates by various mechanisms (chromosomal mutation in the target enzyme, plasmid-mediated acquisition of alternative forms of the target enzymes, reduced permeability of the cell membrane, and altered means of *p*-aminobenzoic acid [PABA] utilization).

### **2.3. Aminoglycosides / Aminocyclitols (Table 2.3)**

#### *Identity (Fig. 2.3)*

Streptomycin, kanamycin, and tobramycin are single-component natural products (purified from different species of *Streptomyces*). Neomycin and gentamicin are mixtures of closely related naturally occurring compounds. Amikacin and netilmicin are semisynthetic derivatives of naturally occurring compounds. The “-micins” and “-mycins” are derived from different organisms. (*Note: there are no drugs with the suffix “-myosin.”*)

#### *Mechanism of Action.*

Aminoglycosides penetrate bacterial cell membranes by means of an energy-dependent carrier mechanism. Once in the bacterial cell, they bind to both subunits of the bacterial ribosome, interfering with their assembly, and causing mRNA to be misread. Because the antibacterial activity of aminoglycosides seems out of proportion to its ability to interfere with protein synthesis, it is believed they also have other sites or mechanisms of action.

#### *Activity*

Aminoglycosides are primarily used against Gram-negative bacteria, although they are also used against Gram-positive bacteria in



**Table 2.3**  
**Currently Marketed Aminoglycoside Antibiotics**

Generic name	O	IV	IM	T	Trade names
Amikacin		X	X		Amikin
Gentamicin		X	X	X	Garamycin, Gentasol, Gentak, Gentagen, Gentafair, Genoptic, Gentacidin
Kanamycin	X	X	X		Kantrex
Neomycin	X		X	X	Duomycin-Hc, <sup>a</sup> Dexasporin, <sup>a</sup> Dexacidin, <sup>a</sup> Cortomycin, <sup>a</sup> Cortisporin, <sup>a</sup> Bio-Cot, <sup>a</sup> Bacitracin, <sup>a</sup> Gatol, <sup>a</sup> Neoptic, <sup>a</sup> Otimar, <sup>a</sup> Oticin, <sup>a</sup> Poly-Pred, <sup>a</sup> Octicair, <sup>a</sup> Npd, <sup>a</sup> Maxitrol, <sup>a</sup> Neosporin, <sup>a</sup> Methadex, <sup>a</sup> Neopolydex, <sup>a</sup> Neodecadron, Neocin, <sup>a</sup> Neocidin, <sup>a</sup> Neo-Fradin, Neomycin, Polymycin, <sup>a</sup> Ak-Trol, <sup>a</sup> Genosporin, <sup>a</sup> Alba <sup>a</sup>
Paromomycin	X				Humatin
Streptomycin			X		
Tobramycin		X	X	X	Aktob, Tobi, Tobradex, Tobrasol, Tobrex, Tomycine, Nebcin

<sup>a</sup>Multicomponent product

O, oral; IV, intravenous, IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears

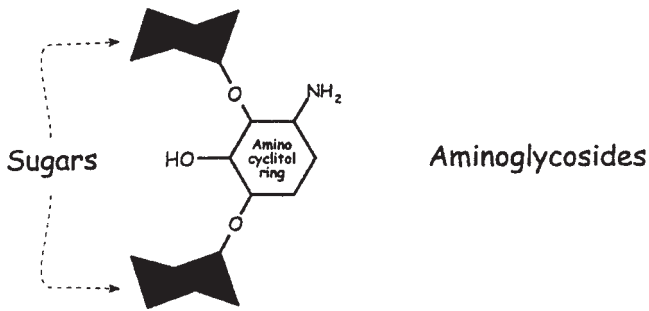


Fig. 2.3

conjunction with cell wall active agents. They have important roles in the treatment of tularemia, bubonic plague, and brucella infections. Some drugs in this class also have activity against mycobacteria. Paromomycin is administered orally for the treatment of intestinal parasitic infections, and parenterally for leishmaniasis.

Aminoglycosides are inactive in acidic or hypoxic environments (e.g., abscess). In some cases (e.g., pseudomonas), aminoglycosides appear to have a significant "post-antibiotic effect". They are often used to suppress the emergence of resistance to other drugs being administered concomitantly, although in most cases this indication is speculative.

#### *Administration, Metabolism, and Elimination*

Drugs in this class are not absorbed from the gastrointestinal tract and they penetrate poorly outside the vascular and interstitial compartments. They are eliminated unchanged into the urine.

Most dosing strategies involve a loading dose that is not corrected for renal function impairment, followed by maintenance doses that are adjusted according to renal function. They have a relatively low therapeutic index, necessitating diligent pharmacokinetic monitoring of blood levels during therapy. Exceeding either the recommended peak or trough levels is associated with increased likelihood of toxicity. The costs of intravenous administration and monitoring make the cost of aminoglycoside therapy relatively high.

*Adverse Effects*

A mild degree of nonoliguric renal failure is common during therapy, but usually reversible. The risk is related to blood levels above target ranges, advanced age, female gender, liver disease, and hypotension.

Damage to both auditory and vestibular branches of cranial nerve VIII is also common, and is usually of greater consequence because it is irreversible.

Aminoglycosides can cause temporary neuromuscular paralysis. This occurs rarely, but can be serious.

*Drug Interactions.*

The risk of neuromuscular paralysis is higher in combination with other agents acting on the neuromuscular junction, e.g., succinylcholine.

*Mechanisms of Resistance*

Enzymatic conjugation is the most common mechanism of resistance. Plasmid-mediated conjugating enzymes are of three types: acetylation, adenylation, and phosphorylation. Note that bacteria conjugate and inactivate aminoglycosides, whereas humans do not alter these drugs prior to elimination in the urine. Different plasmids bearing enzymes with specificities for different aminoglycosides predominate in different hospitals.

There are a large number of enzymes that inactivate gentamicin, but somewhat fewer that inactivate amikacin. This has led to a policy of holding amikacin "in reserve," for use only in cases of proven gentamicin resistance, or when gentamicin resistance has become prevalent. These policies alter the prevalence of different plasmid-encoded enzymes by altering selective pressure.

Bacteria may also resist aminoglycosides by inactivating their influx mechanism. This is a serious problem in some hospitals, but rare in most.

**2.4 Antiribosomal Agents (Table 2.4 and Fig. 2.4)****30S AGENTS: TETRACYCLINE***Identity (Fig. 2.4.1)**Mechanism of Action*

Tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome and inhibit protein synthesis (by interfering with aminoacyl-

**Table 2.4**  
**Currently Marketed Antiribosomal Antibiotics**

<b>Subclass</b>	<b>Generic name</b>	<b>O</b>	<b>IV</b>	<b>IM</b>	<b>T</b>	<b>Trade names</b>
<b>30S subunit target</b> (tetracyclines)	Tetracycline	X	X		X	Actisite, Achromycin, Brodspec, Sumycin, Tetra
	Demeclocycline	X				Declomycin
	Doxycycline	X				Vibramycin, Periostat, Doxycel, Atridox, Doryx, Bio-Tab, Doxal, Doxy-Cap, Vibra- Tabs, Doxy-Tabs, Monodox
<b>30S subunit target</b> (other)	Minocycline	X	X			Vectrin, Dynacin, Minocin
	Oxytetracycline	X	X	X	X	Urobiotic-250, <sup>a</sup> Terramycin, <sup>a</sup> Geomycin
	Spectinomycin			X		Trobicin
<b>50S subunit target</b> (macrolides)	Azithromycin	X	X			Zithromax
	Clarithromycin	X				Biaxin
	Dirithromycin	X				Dynabac
	Erythromycin	X			X	Erythromycin, Akne-Mycin, Erythra, Engel, Erygel, Ery-C, Erytab, Erymax, E-Mycin, Romycin, PCE
	Erythromycin estolate	X				Ilosone
Erythromycin	X				Pediazole, <sup>a</sup> Ees, <sup>a</sup> Pediagen, <sup>a</sup> Erythro-Sul, <sup>a</sup> Eryzole, <sup>a</sup> Eryped	
Ethylsuccinate					Erythrocin <sup>a</sup>	
Erythromycin		X				
Lactobionate						
Erythromycin stearate	X					Erythrocin, <sup>a</sup> Erythrocot
Troleandomycin	X					Tao

<b>50S subunit target</b> (ketolides)	Telithromycin	X		Ketek
<b>50S subunit target</b> (other)	Chloramphenicol	X	X	Chloroptic, Chloromycetin
	Clindamycin	X	X	Cleocin, Clinda-Derm, Clindamycin
	Lincomycin	X	X	Bactramycin, Lincocin, Lincocject
(oxazolidinones)	Linezolid	X		Zyvox
(streptogramins)	Dalfopristin	X		Synercid <sup>a</sup>
	Quinupristin	X		Synercid <sup>a</sup>

<sup>a</sup>Multicomponent product

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears.

## Antiribosomal agents

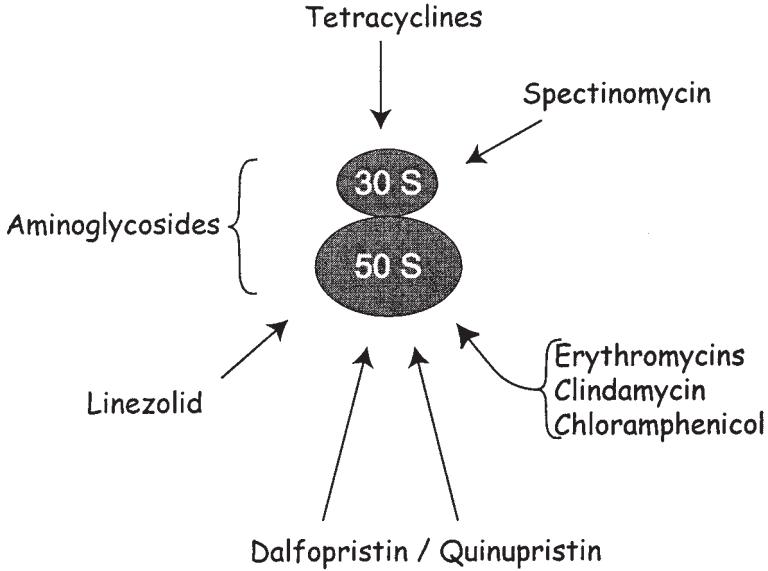


Fig. 2.4

tRNA binding). Their ability to penetrate the outer membrane of Gram-negative bacteria relies on porins. Penetration of the inner membrane is an energy-dependent carrier-mediated process.

### Activity

Many organisms once susceptible are now resistant to tetracyclines, but useful activity remains among many Gram-positive and Gram-negative organisms. They exhibit important activity against *Rickettsia*, *Mycoplasma*, *Chlamydia*, and spirochetes including *Borrelia*. They are also used prophylactically against malaria and travelers' diarrhea.

### Administration, Metabolism, and Elimination

The absorption of tetracyclines from the gastrointestinal tract is carrier mediated, and the capacity of this carrier is readily saturated. As a consequence, their bioavailability decreases with increasing dose.

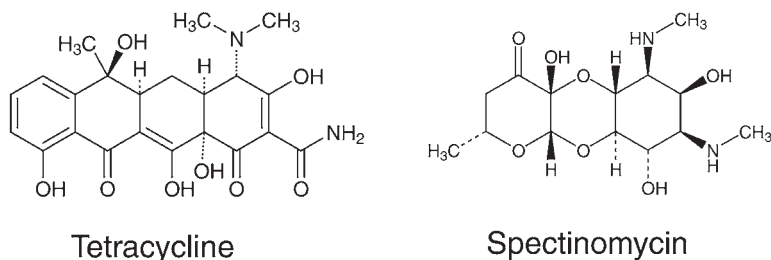


Fig. 2.4.1

They exhibit complex elimination kinetics because of their propensity to bind divalent cations (dairy products, antacids, bone, tooth enamel), and their tendency to be transported via carriers (elimination into saliva, tears, respiratory secretions, as well as urine and bile).

#### *Adverse Effects*

Photosensitivity is of particular importance because these agents tend to be useful when travelling to areas where sun exposure is relatively high. They are contraindicated in pregnancy because their propensity to bind divalent cations (e.g., calcium) results in a discoloration of developing teeth and a depression of bone growth in children. They tend to form nephrotoxic degradation products on long storage (Fanconi's syndrome).

#### *Drug Interactions.*

Decreased absorption with antacids containing calcium and magnesium (i.e., divalent cations).

#### *Mechanisms of Resistance*

Bacteria can resist the action of tetracyclines by losing their influx pump, or by acquiring a plasmid that encodes for an efflux pump.

#### **30S AGENTS: SPECTINOMYCIN**

Spectinomycin is a tricyclic compound often misleadingly grouped with the aminoglycosides, but its structure (Fig. 2.4.1), mechanism of action, and spectrum of activity all differ markedly from the aminoglycosides. It binds to the 30S subunit of the bacterial ribosome. This drug has a single indication: the treatment of gonorrhea in persons for whom other recommended treatments are not safe or available, and for whom a single intramuscular injection is advantageous.

**50S AGENTS: MACROLIDES***Identity*

Macrolides consist of a large 14- or 15-membered ring to which two sugar residues are attached.

*Mechanism of Action*

Macrolides have a dual mechanism of action. They bind to 50S subunit of bacterial ribosome and inhibit protein synthesis by inhibiting transpeptidation and translocation. This binding site overlaps with that of clindamycin and chloramphenicol. They also inhibit the formation of the 50S ribosomal subunit. Delays inherent in the formation of new 50S particles account for prolonged postantibiotic effects (see Section 1.4).

*Activity*

They exhibit broad Gram-positive and Gram-negative activity, with important activity against *Legionella*, mycoplasma, *Chlamydia*, *Rickettsia*, *Helicobacter*, spirochetes, and anaerobes. Spiramycin appears to have some activity against *Cryptosporidium* and *Toxoplasma*. Their antimicrobial activity increases markedly as environmental pH increases from 5.5 to 8.5.

*Administration, Metabolism, and Elimination*

Tissue half-lives are much longer than half-lives in blood, and tissue concentrations may be orders of magnitude higher than blood concentration. For this reason, dosing intervals and duration of action are usually much longer than the serum half-lives (erythromycin, < 2 h; clarithromycin, 5-7 h; azithromycin, 35-40 h).

Erythromycin is degraded by stomach acid (the ester linkage in the ring is acid-labile), and causes phlebitis when administered intravenously [due to the basic  $N(CH_3)_2$  group on one of its sugars]. For oral administration, acid-stable stearate, estolate, and ethylsuccinate conjugates are available. For intravenous administration, gluceptate and lactobionate salts are more soluble and less likely to cause phlebitis.

*Adverse Effects*

Gastrointestinal disturbance is common with all forms of erythromycin, but it is less common or less severe with clarithromycin and



azithromycin. The cause of this disturbance is related to the stimulation of gut receptors for motilin, a hormone regulating gut motility.

#### *Drug Interactions*

Macrolides decrease hepatic metabolism and increase the pharmacological effects of many drugs (including warfarin, prednisone, theophylline, cyclosporin, carbamazepine, digoxin). Macrolides antagonize the action of chloramphenicol and clindamycin due to their overlapping binding sites on the ribosome.

#### *Mechanisms of Resistance*

Bacteria resist macrolide action by a variety of mechanisms including reduced permeability, active efflux, enzymatic digestion, and chromosomal mutations that alter protein or RNA in the ribosomal binding site. In addition to these mechanisms, there is a gene that confers macrolide resistance by methylating ribosomal RNA. The presence of this gene is associated with resistance to clindamycin and streptogramins as well as both macrolides and ketolides.

### **50S AGENTS: KETOLIDES**

With the introduction of telithromycin, ketolides become the newest class of antimicrobial drugs available in the United States. Ketolides are closely related to macrolides in structure (**Fig. 2.4.2**), and share a similar dual mechanism of action. However, telithromycin is active against many organisms that are resistant to erythromycin, although it may not be effective against some species in which macrolide resistance is due to methylated ribosomal RNA.

### **50S AGENTS: CHLORAMPHENICOL**

#### *Identity (Fig. 2.4.3)*

Chloramphenicol is the least expensive and most widely available antimicrobial agent in underdeveloped countries.

#### *Mechanism of Action.*

Chloramphenicol penetrates the microbial membrane by an energy-dependent influx mechanism and binds to the 50S subunit of bacterial ribosomes, inhibiting protein synthesis. Its binding site overlaps that of erythromycin and clindamycin.

#### *Activity*

Chloramphenicol exhibits diverse activity against Gram-negative and Gram-positive organisms, especially anaerobes. It has especially

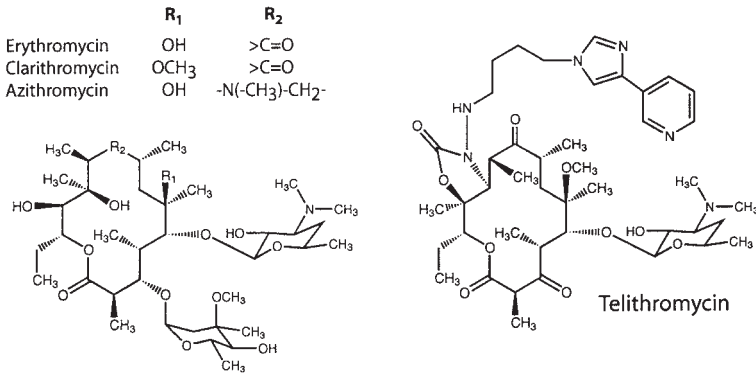


Fig. 2.4.2

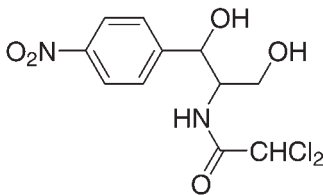
important activity against rickettsia, mycoplasma, and spirochetes, and is also used for the treatment of deep abscesses, Typhoid Fever, Rocky Mountain Spotted Fever, and infections due to vancomycin-resistant enterococci.

#### *Administration, Metabolism, and Elimination*

The bioavailability of chloramphenicol is high, and it readily penetrates all body tissues, as well as abscess cavities. It is inactivated by conjugation in the liver.

#### *Adverse Effects.*

Chloramphenicol reliably causes reversible dose-related bone marrow suppression, probably due to interference with protein synthesis by mitochondrial ribosomes.



Chloramphenicol

Fig. 2.4.3

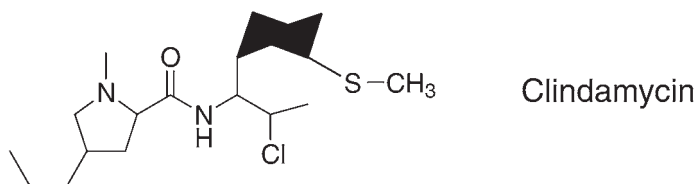


Fig. 2.4.4

In contrast, it also causes irreversible idiosyncratic aplastic anemia that is fatal without bone marrow transplant. Most of these reactions follow oral administration, suggesting that a metabolic product of intestinal bacteria may be responsible. Incidence is between 1/25,000 and 1/40,000 patients.

#### *Drug Interactions*

Chloramphenicol inhibits the metabolism of many other drugs by microsomal enzymes, thereby prolonging the action of oral hypoglycemic agents, phenytoin, cyclophosphamide, and warfarin. It antagonizes the action of macrolides and clindamycin due to their overlapping binding sites on the ribosome.

#### *Mechanisms of Resistance.*

Bacteria may resist the action of chloramphenicol by shutting down their influx mechanism, or by acquiring a plasmid encoding for chloramphenicol acetyltransferase.

#### **50S AGENTS: CLINDAMYCIN**

#### *Identity (Fig. 2.4.4)*

#### *Mechanism of Action*

Clindamycin binds to the 50S subunit of bacterial ribosomes and inhibits protein synthesis. Its binding site overlaps that of erythromycin and chloramphenicol.

#### *Activity*

Clindamycin has important activity against Gram-positive and Gram-negative anaerobes *Babesia* and *Toxoplasma*. Occasionally, it is also used against methicillin-resistant *S. aureus*, and other Gram-positive aerobes.

*Administration, Metabolism, and Elimination*

Clindamycin is well absorbed, metabolized in the liver to the *N*-demethyl form, and eliminated into the bile. *N*-demethyl clindamycin has more activity than its parent compound, and has major effects on bowel flora. For intravenous administration, clindamycin is administered as the phosphate ester which is rapidly hydrolyzed in vivo. A tendency to concentrate in bone makes clindamycin a favored agent for the treatment of osteomyelitis.

*Adverse Effects*

Clindamycin therapy is frequently accompanied by diarrhea, but mild and uncomplicated diarrhea (antibiotic-associated diarrhea) must be distinguished from pseudomembranous or antibiotic-associated colitis (AAC), a serious and even life-threatening condition. AAC is caused by toxins from *C. difficile*, which overgrows the colonic flora during clindamycin therapy. The incidence is reported to vary from 1/10 to 1/10,000 in different studies. Classically, AAC is caused by clindamycin, but may also be caused by any antibiotic that alters the normal colonic bacterial flora. It is treated by discontinuing the precipitating antibiotic, and the oral administration of vancomycin or metronidazole.

*Drug Interactions*

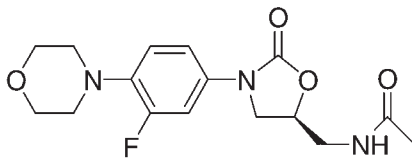
Clindamycin antagonizes the action of macrolides and chloramphenicol due to their overlapping binding sites on the ribosome. It may prolong the action of neuromuscular blocking agents.

*Mechanisms of Resistance*

Resistance is most commonly due to altered ribosomal proteins and ribosomal RNA. These alterations typically exhibit cross-resistance to erythromycin and chloramphenicol.

**50S AGENTS: OXAZOLIDINONES***Identity (Fig. 2.4.5)**Mechanism of Action*

Oxazolidinones bind to the 50S subunit of the bacterial ribosome and inhibit protein synthesis by preventing the initiation of mRNA translation.



Linezolid

Fig. 2.4.5

### *Activity*

This class of antibiotics was developed to target vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, and drug resistant *S. pneumoniae*.

### *Administration, Metabolism, and Elimination*

Well absorbed orally; oral administration achieves the same blood levels as intravenous administration.

### *Adverse Effects*

Information about safety profile is limited, but various forms of myelosuppression appear to be common with prolonged administration.

### *Drug Interactions*

Linezolid is an inhibitor of monoamine oxidase and may therefore elevate blood pressure in persons taking pseudoephedrine or phenylpropanolamine.

### *Mechanisms of Resistance*

Gram positive resistance due to mutations in ribosomal RNA have been reported. Gram-negative bacteria appear to have an active efflux mechanism.

## **50S AGENTS: STREPTOGRAMINS**

### *Identity (Fig. 2.4.6)*

Streptogramins are produced in nature as synergistic pairs. Naturally occurring pristinamycin/virginiamycin is used in Europe. Quinupristin and dalfopristin comprise a pair of semisynthetic derivatives marketed in the United States as Synercid.

### *Mechanism of Action*

Streptogramins bind to two different sites on the 50S subunit of the bacterial ribosome, and inhibit protein synthesis at two different

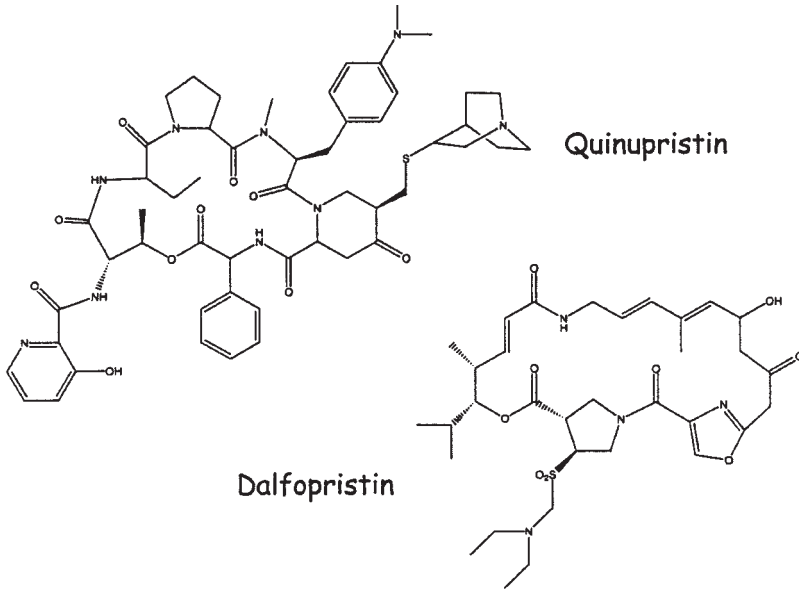


Fig. 2.4.6

stages, thereby exerting strongly synergistic activity. Binding of quinupristin increases the affinity of dalfopristin for its binding site, and their combined action is irreversible.

#### Activity

Streptogramins are active against *E. faecium* (including vancomycin-resistant strains), but it is important to note that they are not active against *E. faecalis*. They may also be used against some staphylococcal and streptococcal infections.

#### Administration, Metabolism, and Elimination

These agents require intravenous administration.

#### Adverse Effects

Severe arthralgias and myalgias are common.

#### Drug Interactions

Inhibits a widely used hepatic P450 enzyme (CYP 3A4), and is therefore likely to interact with many other drugs.

**Table 2.5**  
**Currently Marketed Topoisomerase Inhibitors**

Generic name	O	IV	IM	T	Trade names
Alatrofloxacin		X			Trovan
Cinoxacin	X				Cinobac
Ciprofloxacin	X	X		X	Cipro, Ciloxan
Enoxacin	X				Penetrex
Gatifloxacin	X	X			Tequin
Grepafloxacin	X				Raxar
Levofloxacin	X	X			Levaquin
Lomefloxacin	X				Maxaquin
Moxifloxacin	X				Avelox
Norfloxacin	X			X	Noroxin, Chibroxin
Ofloxacin	X	X		X	Floxin, Ocuflox
Sparfloxacin	X				Zagam
Trovafloxacin	X				Trovana

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears

### *Mechanisms of Resistance*

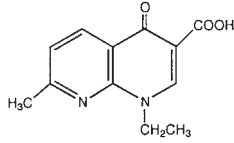
Cross-resistance with erythromycin/clindamycin, intracellular degradation, and efflux mechanisms have been reported. The occurrence of primary resistance to streptogramins as a class has been linked to the use of virginiamycin as an animal growth promoter in Europe.

## **2.5 Topoisomerase Inhibitors (Quinolones, Table 2.1.5)**

### *Identity (Fig. 2.5)*

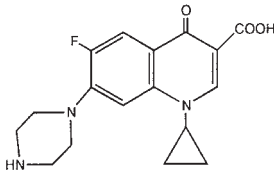
The quinolones are chemically related to nalidixic acid, an antimicrobial introduced more than 40 y ago for urinary tract infections. The key modification that led to more potent agents was the addition of a fluorine atom, so they are also known as fluoroquinolones.

Purification of the “levo-” stereoisomer of ofloxacin from a racemic mixture of levo and the inactive “dextro-” form yields levofloxacin—a preparation with twice the antimicrobial potency of ofloxacin. Alatrofloxacin is a prodrug form of trovafloxacin intended for intravenous administration.

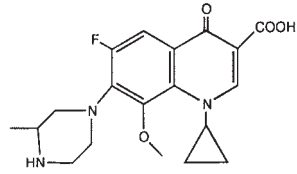


Nalidixic acid

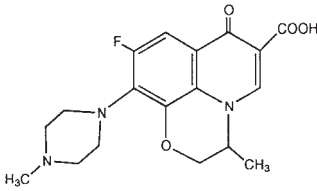
## Quinolones



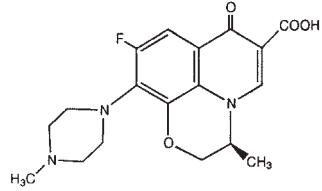
Ciprofloxacin



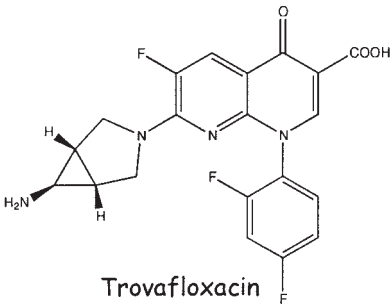
Gatifloxacin



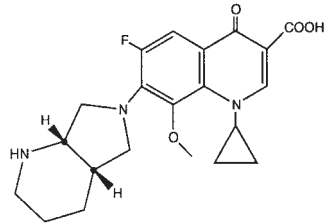
Ofloxacin



Levofloxacin



Trovafloxacin



Moxifloxacin

Fig. 2.5



*Mechanism of Action*

Quinolones inhibit DNA synthesis by inhibiting two topoisomerases that are essential to bacterial replication: DNA gyrase, which induces supercoiling of the chromosome, and topoisomerase IV, which helps divide replicated chromosomes.

*Activity*

Quinolones exhibit broad activity against Gram-negative and Gram-positive organisms, although it is highly variable among different agents in this class. Some of these antibiotics exhibit important activity against *Pseudomonas*, *Xanthomonas*, chlamydia, and some mycobacteria.

*Administration, Metabolism, and Elimination*

Although their bioavailability is generally good, some agents (nalidixic acid, norfloxacin) achieve therapeutic concentrations only in the urine.

*Adverse Effects*

Quinolones are generally well tolerated, but relatively contraindicated in children due to possible effects on mineralization of cartilage.

*Drug Interactions*

Their absorption from the gastrointestinal tract is hindered by antacids and iron/zinc-containing multivitamins. They also reduce the elimination of theophylline.

*Mechanisms of Resistance*

Resistant bacteria often have mutations in the target enzyme, but more complex resistance mechanisms also appear to be present.

**2.6 Miscellaneous Agents (Table 2.6)****METRONIDAZOLE*****Identity (Fig. 2.6.1)****Mechanism of Action*

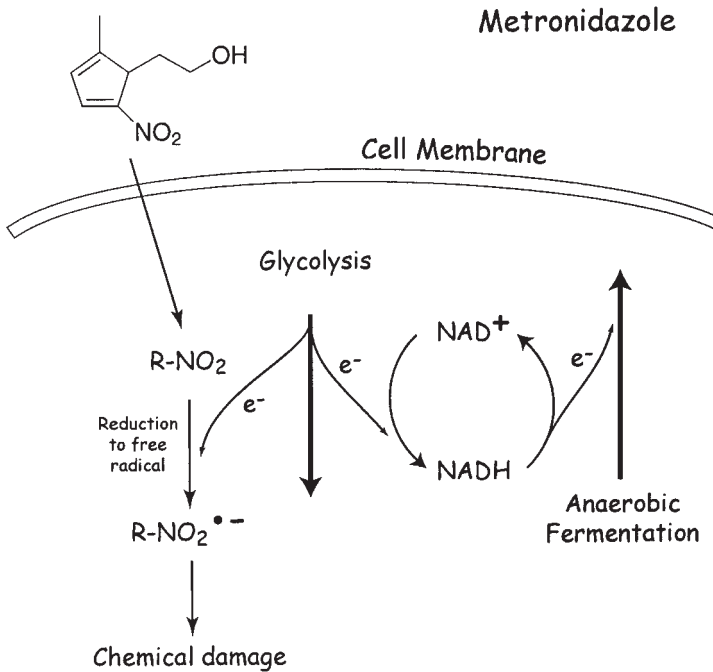
Under anaerobic conditions, metronidazole is activated by a bacterial enzyme that reduces (adds an electron to) the NO<sub>2</sub> group. This has two consequences. First, it converts the drug into a highly reactive free radical that damages various proteins and nucleic acids by forming chemical adducts. This traps converted drug in the cell, so there

**Table 2.6**  
**Miscellaneous Currently Marketed Antibiotics**

Generic name	O	IV	IM	T	Trade names
Bacitracin			X	X	Neosporin, <sup>a</sup> Neocin, <sup>a</sup> Baciim, Polysporin, <sup>a</sup> Cortomycin, <sup>a</sup> Cortisporin, <sup>a</sup> Neocidin, <sup>a</sup> Polycidin, <sup>a</sup> Neomycin, <sup>a</sup> Ocumycin, <sup>a</sup> Triple-antibiotic, <sup>a</sup> Polymycin, <sup>a</sup> Polytracin, <sup>a</sup> Polycin <sup>a</sup>
Gramicidin				X	Neosporin, <sup>a</sup> Triple-antibiotic, <sup>a</sup> Alba, <sup>a</sup> Neomycin, <sup>a</sup> Neocin, <sup>a</sup> Polymycin, <sup>a</sup> Neoptic, <sup>a</sup> Neocidin <sup>a</sup>
Metronidazole	X	X		X	Flagyl, Noritate, Metrocream, Metrogel, Metron
Mupirocin				X	Bactroban
Polymyxin		X	X	X	Triple-antibiotic, <sup>a</sup> Cortisporin, <sup>a</sup> Duomycin-Hc, <sup>a</sup> Dexacidin, <sup>a</sup> Cortomycin, <sup>a</sup> Gatol, <sup>a</sup> Terramycin, <sup>a</sup> Genosporin, <sup>a</sup> Dexasporin, <sup>a</sup> Oticin, <sup>a</sup> Poly-Pred, <sup>a</sup> Otimar, <sup>a</sup> Methadex, <sup>a</sup> Otobiotic, Polymixin, Npd, <sup>a</sup> Neo, <sup>a</sup> Neopolydex, <sup>a</sup> Polytrim, <sup>a</sup> Alba, <sup>a</sup> Neoptic, <sup>a</sup> Bio-Cot, <sup>a</sup> Polycin, <sup>a</sup> Bacitracin, <sup>a</sup> Polymycin, <sup>a</sup> Neomycin, <sup>a</sup> Neocin, <sup>a</sup> Polysporin, <sup>a</sup> Neocidin, <sup>a</sup> Maxitrol, <sup>a</sup> Neosporin, <sup>a</sup> Polytracin, <sup>a</sup> Octicair, <sup>a</sup> Polycidin, <sup>a</sup> Ak-Trol, <sup>a</sup> Ocumycin <sup>a</sup>

<sup>a</sup>Multicomponent product

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears



Metronidazole exerts two deleterious effects on anaerobic bacteria and protozoan parasites. First, upon reduction to a negatively charged highly reactive free radical, it chemically attacks diverse cellular materials and destroys their normal function. Because it is readily reduced and binds irreversibly to cell materials, diffusion into the cell is nearly an irreversible process. Second, it consumes the reducing capacity of the cell, inhibiting the reduction of NAD<sup>+</sup> to NADH which is needed for anaerobic fermentation.

Fig. 2.6.1

is a continuous gradient across the cell membrane from outside to inside, and biochemical damage accumulates. Second, this reaction competes for the reduction of NAD<sup>+</sup>, and deprives the anaerobic cell of needed NADH.

*Activity*

Metronidazole is highly active against many Gram-negative anaerobes, but it is inconsistently effective against Gram-positive anaerobes. It has important activity against *C. difficile*, *Helicobacter*, and several protozoa including trichomonas, ameba, and giardia.

*Administration, Metabolism, and Elimination*

Metronidazole is well absorbed and distributes well throughout all compartments including the cerebrospinal fluid and into abscesses.

*Adverse Effects*

Disulfiram-like reaction with alcohol. Glossitis and metallic taste. Neurotoxicity: seizures, encephalopathy, ataxia, and peripheral neuropathy.

*Drug Interactions*

Minor.

*Mechanisms of Resistance*

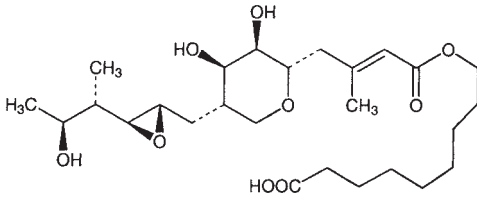
Resistance arises presumably as a result of the inactivation or loss of the enzyme that reduces the NO<sub>2</sub> group.

**MUPIROCIN**

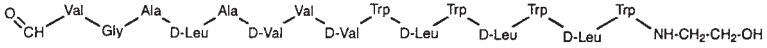
Mupirocin is a bacterial product purified for topical use (**Fig. 2.6.2**). It inhibits protein synthesis (by inhibiting the tRNA synthase for isoleucine), and its spectrum of action includes a variety of common Gram-positive skin pathogens, but not the normal flora of skin.

**POLYPEPTIDES**

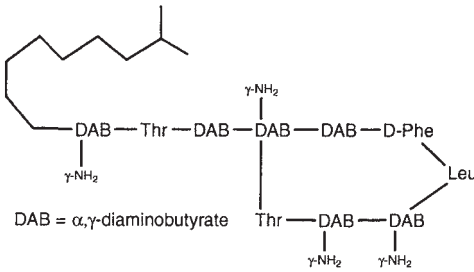
Polypeptide antibiotics (**Fig. 2.6.2**) are ubiquitous in nature, and they even play a vital role in the host defense systems of humans. In most cases, their mechanisms of action are poorly defined, although they appear in general to alter membrane permeabilities. The action of gramicidin A is relatively well understood to be due to the formation of sodium ion channels. Systemic use is precluded by toxicity, but bacitracin, polymyxin B, and gramicidin have been widely employed for topical use. Being foreign polypeptides, these agents exhibit a high incidence of hypersensitivity reactions. This may be encountered in unexpected circumstances when small amounts of these compounds are included as preservatives in vaccines or other parenteral preparations.



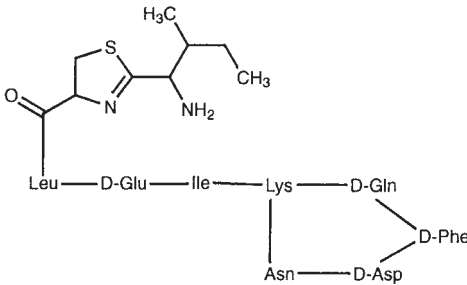
Mupirocin



Gramicidin A



Polymyxin B



Bacitracin

Fig. 2.6.2

**Table 2.7**  
**Currently Marketed Antimycobacterial Agents**

Generic name	Oral	IV	IM	Trade names
Aminosalicylic acid	X			Paser
Capreomycin		X	X	Capastat
Clofazimine	X			Lamprene
Ethambutol	X			Myambutol
Ethionamide	X			Trecator
Isoniazid	X		X	Rifater, <sup>a</sup> Nydrazid, Rifamate <sup>a</sup> Tubizid
Pyrazinamide	X			Rifater <sup>a</sup>
Rifabutin	X			Mycobutin
Rifampin	X	X		Rifamate, <sup>a</sup> Rifadin, Rimactane, Rifater
Rifapentine	X			Priftin

\* Multicomponent product

O, oral; IV, intravenous; IM, intramuscular; T, topical, including preparations applied to skin, eyes, and ears

## 2.7 Antimycobacterial Agents (Table 2.7)

Drugs used for the treatment of tuberculosis have long been divided into first-line agents having relatively high efficacy and low toxicity, and second-line agents with either lower efficacy, higher toxicity, or both. Because resistance to any single agent arises spontaneously in a predictable fraction of organisms, but the likelihood that organisms will arise with simultaneous resistance to multiple agents is much lower, it is recommended that treatment always be initiated with multiple agents, particularly in cavitary lung disease where the numbers of organisms present may be large. For the same reason, drugs in a failing multidrug regimen are not replaced one at a time, but instead replaced with a new regimen incorporating at least two new drugs.

A distinction is made between the treatment of "active" or clinically apparent disease, and "latent" or subclinical disease. The latter is detected by a positive tuberculin skin test in someone who has not received effective antituberculous therapy. The treatment of subclinical infection is often referred to as "prophylaxis" or "prophylactic

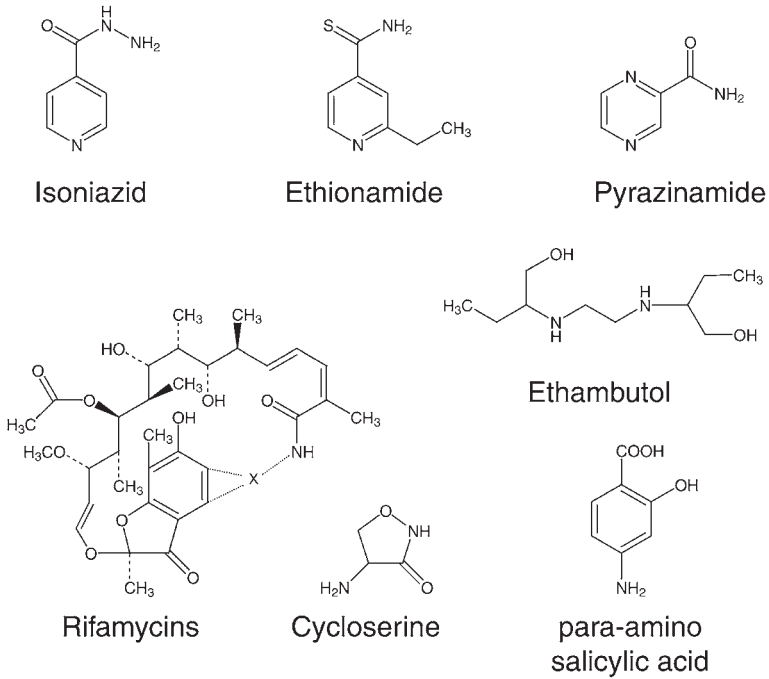


Fig. 2.7

treatment” because it is aimed at preventing disease due to the reactivation of dormant tubercle bacilli later in life.

#### FIRST LINE AGENTS: ISONIAZID (INH)

##### *Identity (Fig. 2.7)*

##### *Mechanism of Action*

INH must be activated by a bacterial enzyme. The activated drug inhibits a key enzyme involved in mycolic acid synthesis

##### *Activity*

INH is an agent of choice for the treatment of latent infection and of active disease. The treatment of latent infection is generally prompted by a positive skin test with purified protein derivative (PPD) in the absence of evidence of active infection. Under these circumstances,

the number of organisms present is believed to be sufficiently low to permit INH treatment of latent infection without problems arising due to INH resistance.

#### *Administration, Metabolism, and Elimination*

INH is acetylated by the liver and then eliminated into the urine. There is a bimodal distribution of genetic traits for rapid and slow rates of acetylation, but therapeutically adequate blood levels can be maintained with daily therapy even with rapid acetylators.

#### *Adverse Effects*

INH therapy is associated with a hepatotoxicity that may become life threatening, and whose incidence strongly correlates with age. It is also associated with peripheral neuropathy, whose incidence is strongly correlated with slow acetylation. Neuropathy is usually prevented by concomitant treatment with pyridoxine (vitamin B6).

#### *Drug Interactions*

There are numerous interactions between INH and other drugs, particularly in slow acetylators. Concomitant use of rifampin increases likelihood of hepatotoxicity.

#### *Resistance*

Resistance arises via single step mutation in the activating enzyme. Mutations in the target enzyme (which confer cross-resistance to ethionamide) are less common.

### **FIRST LINE AGENTS: RIFAMYCINS**

#### *Identity (Fig. 2.7)*

Rifamycins are complex bacterial products. Rifampin, rifapentine, and rifabutin (ansamycin) are semisynthetic derivatives.

#### *Mechanism of Action*

Rifamycins inhibit transcription (chain initiation by bacterial DNA-dependent RNA polymerase).

#### *Activity*

Rifamycins have broad antibacterial, antifungal, antiparasitic, and even antiviral activity. Rifampin is used as a single agent for prophylaxis against *N. meningitidis*, but it is not otherwise used as a single agent owing to rapid emergence of resistance. Its most important role is in multidrug programs for treating *M. tuberculosis*, and it



may be used in combination with pyrazinamide for the treatment of latent infection (prophylactic treatment). Rifampin is also used occasionally to synergize with  $\beta$ -lactams against staphylococci and with amphotericin against candida. Rifabutin exhibits activity against some strains of *M. tuberculosis* that are resistant to rifampin, and it has better activity than rifampin against *M. avium* complex. Rifapentine has a longer half-life permitting less frequent dosing.

#### *Administration, Metabolism, and Elimination*

Rifamycins exhibit complex kinetics including autoinduction of metabolizing enzymes and interactions with isoniazid.

#### *Adverse Effects*

Rifamycins are associated with numerous adverse effects. All patients experience an orange-red coloration of the urine and tears that tends to permanently stain contact lenses. Many develop skin exanthems of varying severity and flu-like syndromes with long term treatment. Some develop hepatotoxicity and thrombocytopenia. Rifamycins increase the likelihood of hepatitis in patients treated with isoniazid.

#### *Drug Interactions*

Rifamycins induce hepatic microsomal enzymes leading to decreased effect of many drugs.

#### *Resistance*

Single step mutation in the target enzyme is common.

### **FIRST-LINE AGENTS: PYRAZINAMIDE (PZA)**

PZA is a synthetic compound, similar to isoniazid and ethionamide in structure (**Fig. 2.7**), and also similar in that it must be activated by cellular enzymes. These enzymes are peculiar to *M. tuberculosis*, so that PZA is not effective against other mycobacteria. Loss of its activating enzyme results in resistance. Although the target of the activated drug is not known, PZA is of proven value as a component of multidrug therapy for *M. tuberculosis* with a particular effectiveness against semidormant organisms. PZA can cause hyperuricemia. It also is associated with hepatotoxicity although it is not clear that this should be attributed to PZA because INH or rifampin are almost always given concomitantly, and these agents are hepatotoxic apart from PZA.

**FIRST-LINE AGENTS: ETHAMBUTOL (EMB)**

EMB is a simple synthetic compound (**Fig. 2.7**) that inhibits an enzyme involved in cell wall biosynthesis. It has proven value as a component of multidrug therapy for *M. tuberculosis*, but tends to cause optic neuritis with impairment of visual acuity and color vision at high doses.

**FIRST-LINE AGENTS: AMINOGLYCOSIDES**

Streptomycin was the first aminoglycoside antibiotic to be used in humans (Section 2.3) and it shares most properties of other drugs in this class including their toxicities. Due to initial problems with vestibular toxicity when administered intravenously, it is now administered only via intramuscular injection. However, the tendency of streptomycin to cause this toxicity may not be greater than that of other aminoglycosides. It is highly active against *M. tuberculosis*, but is limited in its overall therapeutic efficacy because it is unable to reach intracellular organisms. Amikacin and kanamycin are also effective, but usually considered second line agents for historical reasons and relative cost.

**SECOND-LINE AGENTS: QUINOLONES**

Quinolones (*see* Section 2.5) are being used with increasing frequency against *M. tuberculosis*, *M. avium* complex, and rapidly growing mycobacteria.

**SECOND LINE AGENTS: PARAAMINOSALICYLIC ACID (PAS)**

PAS (**Fig. 2.7**) impairs folate synthesis but has weak antibacterial activity. Its limiting adverse effect is gastrointestinal disturbance.

**SECOND-LINE AGENTS: CYCLOSERINE**

Cycloserine (**Fig. 2.7**) is an analog of D-alanine that inhibits intracellular stages of cell wall biosynthesis (see discussion of glycopeptide antibiotics, above). It is associated with a high incidence of adverse effects, especially peripheral neuropathy and CNS/psychiatric disturbances.

**SECOND-LINE AGENTS: ETHIONAMIDE (ETH)**

ETH (**Fig. 2.7**) is activated by a different enzyme than INH, but the activated drug inhibits the same enzymes responsible for mycolic acid synthesis as INH. Its limiting adverse effect is gastrointestinal disturbance.

**OTHER SECOND-LINE AGENTS**

Other compounds used against *M. tuberculosis* include capreomycin and viomycin (both cyclic polypeptides) and thiacetazone (a low-cost synthetic compound widely available in underdeveloped countries).

Clofazimine is a complex dye with an unknown mechanism of action, used primarily as part of combination therapy against *M. leprae*.

$\beta$ -lactams are active against the cell wall synthesizing enzymes of mycobacteria, but most mycobacteria resist this action by producing  $\beta$ -lactamases.  $\beta$ -Lactamase resistant cephalosporins are effective against rapidly growing mycobacteria, but not when the organisms are situated intracellularly ( $\beta$ -lactams cannot penetrate cell membranes.)

Macrolides are frequently active against various nontuberculous mycobacteria, and are especially useful in the prophylaxis and treatment of infections with *M. avium* complex.

Antifolate agents have activity against rapidly growing mycobacteria. The most important agent in this class is dapsone for its activity against *M. leprae*.

**MULTIDRUG THERAPY AND MULTIDRUG RESISTANCE IN *M. TUBERCULOSIS***

Mutations that confer resistance to the drugs used for treating tuberculosis occur spontaneously with a rate of  $10^{-3}$ – $10^{-8}$ . Cavitory tuberculosis infections often involve more than  $10^9$  bacilli, and thus one can presume that organisms resistant to any one drug are present at the beginning of therapy. Therapy is usually initiated with multiple first-line agents because the probability of encountering spontaneous resistance to two or more drugs is the product of their individual probabilities. For example, one commonly used regimen consists of INH, rifampin, PZA, and EMB given for 2 m, followed by INH and rifampin for an additional 4 m. The choice of therapy in any particular individual, however, must consider local resistance patterns and any concomitant illness (such as HIV infection). When patient compliance with a prescribed treatment program is unreliable, threats to public health must be considered. Directly observed therapy (DOT) programs have been of proven value in such cases.

“Multidrug resistant” (MDR) tuberculosis is an infection with organisms resistant to INH and rifampin. Oftentimes, these organisms are resistant to other commonly used agents as well. MDR organisms tend to arise by serial selection of resistant mutants, as would occur

when adding single agents to a failing treatment program, or when patient compliance is irregular.

## 2.8 Investigational Agents

New drugs are in development in each of the drug classes described above. In addition, several compounds belonging to entirely new drug classes are in development.

### ADHESION BLOCKING AGENTS

There appears to be a potential for significant therapeutic value in blocking the mechanisms by which bacteria adhere to host tissues. Monoclonal antibodies directed against bacterial adhesins, and analogs of both bacterial adhesins and the adhesin targets of host tissues have demonstrated remarkable effectiveness in both animal and human models, including models of dental caries, candidiasis, various respiratory pathogens, and *Helicobacter* infections of the gut lumen.

### DEFORMYLASE INHIBITORS

Bacteria synthesize proteins with a formyl (HCO-) group on the amino terminus that must be removed in most cases to form fully functional proteins. Inhibitors of deformylase such as actinonin are potentially antibacterial, and are being developed as therapeutic agents.

### DAPTOMYCIN

Daptomycin is a novel cyclic lipopeptide antibiotic that exerts its antibacterial effect at the bacterial cytoplasmic membrane and disrupts multiple aspects of membrane function, including peptidoglycan synthesis, lipoteichoic acid synthesis, and the bacterial membrane potential. Its mechanism of antimicrobial action is distinct from that of other antibiotics, including  $\beta$ -lactams, aminoglycosides, glycopeptides, and macrolides. It is being developed for the treatment of Gram-positive infections such as staphylococci and enterococci.

### EFFLUX PUMP INHIBITORS

Many instances of antimicrobial resistance are due to the active efflux of drugs from the bacterial cell by transmembrane energy-dependent pumps. Inhibitors of these pumps are being devel-

oped, with the intention of using them to suppress resistance to a co-administered antimicrobial agent.

#### **EVERNINIMYCINS**

Everninimycins (or everninomycins) belong to a class of oligosaccharide antibiotics with activity against Gram-positive bacteria. They bind to the 50S ribosomal subunit at a site distinct from currently available 50S-acting agents and inhibit protein synthesis. Unfortunately, one drug in this class—avilamycin—has been used extensively in Europe as an animal growth promoter and colonization of animals with bacteria resistant to both avilamycin and other everninimycins is prevalent. Possibly for this reason, the development of everninimycins for clinical use has been halted.

#### **GLYCOPEPTIDES**

Agents are under development that work by the same mechanism as vancomycin, but are effective against vancomycin resistant enterococci.

#### **GLYCYLCYCLINES**

Glycylcyclines are chemically related to tetracyclines, but will be designed to overcome tetracycline resistance among common respiratory pathogens.

#### **POLYPEPTIDES**

Polypeptides modeled after naturally occurring polypeptides known as “magainins” and “protegrins” are being developed for therapeutic use. Being foreign polypeptides, they are susceptible to digestion if given orally, and may be immunogenic if given parenterally. Current development is focused on topical agents and peptidomimetics that circumvent the problems inherent to ordinary polypeptides.

#### **RAMOPLANIN**

Ramoplanin is a complex natural product that binds to a membrane-anchored intermediate in cell wall biosynthesis and prevents its incorporation into peptidoglycan. Ramoplanin is highly effective against vancomycin-resistant enterococci, and is being developed for oral and topical administration to eliminate colonization by this organism in vulnerable populations.

## 2.9 Combination Antibacterial Therapy

There are four principal indications for using two or more antibiotics simultaneously to treat a patient with an infection.

1. Antibiotic combinations can prevent the emergence of resistance. This strategy is of proven value in the treatment of mycobacterial infections, and in the use of cotrimoxazole for various infections. However, this is not a universal advantage of combination therapy, and it is frequently cited to justify combination antibiotic therapy in situations where clinical data do not support this rationale.
2. In cases of polymicrobial infection combination therapy may be necessary because it is often not possible to choose a single antibiotic that is effective against all of the organisms that are present.
3. It is often the case that empiric treatment must be started while awaiting laboratory identification of the infecting organism. In these cases, it is often justifiable to begin therapy with a combination of antibiotics so that the possibility of treating with no effective agents is reduced.
4. Clinically useful synergism between antibiotics has been demonstrated in several clinical situations. However, not all synergy that is expected can be demonstrated in a laboratory, and not all that can be demonstrated is clinically useful.

Regardless of the indication, there are three disadvantages to combination antibiotic therapy in most clinical situations: it increases the number and likelihood of adverse effects or drug–drug interactions, there are additive costs, and there is the risk of unanticipated antagonism.

## 2.10 Choosing and Planning Antimicrobial Therapy

Historical information is needed before treatment planning to evaluate the likelihood of a bacterial infection, or the justification for prophylactic treatment. Once a need for treatment has been established, additional historical information is needed to ascertain the existence and nature of any hypersensitivity reactions, the most likely source of the infection (community, hospital, foreign), and host factors affecting antibiotic choice (coinfection with human immunodeficiency virus, immunosuppressive treatments, pregnancy,

extreme age, recent prior antibiotic treatment). Finally, one adds local experience, epidemiological information, and formulary guidelines to this historical information and chooses among the subset of available antibiotics that have an appropriate spectrum of activity and the ability to penetrate to the site of the infection.