

Antibiotics Review

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Faculty

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Faculty Disclosure

Contributing faculty, Donna Coffman, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners Disclosure

The division planners have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including physicians, physician assistants, nurses, and nurse practitioners.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide a review of the classes of antibiotics and their characteristics as well as an overview of the individual antibiotics that are currently available for use by the practitioner.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the general characteristics of antibiotics and antibiotic resistance.
2. Outline strategies to combat the development of microbial resistances.
3. Discuss the mechanism of action, pharmacokinetics, and effects of penicillins.
4. Identify the available cephalosporins and their associated characteristics.
5. Describe the other beta-lactams, including the carbapenems and monobactams.
6. Discuss the characteristics of the aminoglycosides, macrolides, and telithromycin.
7. Outline the mechanism of action, pharmacokinetics, and effects of the quinolones and the sulfonamides.
8. Describe the various tetracyclines.



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The number of antibiotic agents available is remarkable, and new agents are frequently added. This course is intended as an overview of the general characteristics of the major antibiotic classes, with a brief discussion of the individual agents and indications, giving greater perspective to the actions and characteristics of antibiotics. Due to the large number of antibiotics available, this course focuses on 8 major classes of antibiotics: the penicillins, cephalosporins, other beta-lactams, aminoglycosides, macrolides, quinolones, sulfonamides, and tetracyclines. Many very useful and commonly used antibiotics are unique and do not fit in these classes and so are not discussed.

It is beyond the scope of this course to define all of the possible side effects, recommended uses, and off-label uses of the antibiotics. Before using a specific antimicrobial, review the manufacturer's package insert and dosing recommendations for the drug.

GENERAL CHARACTERISTICS OF ANTIBIOTICS

There are some characteristics that all antibiotics share. All antibiotics can elicit allergic responses, although some are more allergenic than others. Allergic reactions can range from mild, annoying rashes to life-threatening reactions like anaphylaxis and Stevens-Johnson syndrome. In some cases, there is a cross-sensitivity between agents in different classes. In addition, all antibiotics target normal body flora as well as pathogens, which may result in overgrowth of *Candida* and pathogenic bacteria such as *Clostridium difficile*.

Overgrowth of *C. difficile* is a serious complication of antimicrobial therapy that can produce symptoms ranging from mild diarrhea to severe, life-threatening complications, such as pseudomembranous colitis [1]. Most cases resolve with supportive care and discontinuation of the offend-

ing antibiotic, but many require treatment. In addition, diarrhea and pseudomembranous colitis can develop weeks after antimicrobial therapy has been discontinued. A high degree of suspicion and judicious use of laboratory testing are the keys to recognizing and managing these complications.

ANTIBIOTIC RESISTANCE

Bacteria develop resistance to antibiotics in a variety of ways, including methods that may decrease the intracellular concentrations of the antibiotic, deactivate the antibiotic, change the binding sites for the antibiotic, and develop adaptations that bypass the need for the binding site targeted by the antibiotic [2].

Methods that decrease intracellular concentrations of the antibiotic include changes in the cell wall to increase the efflux of the antibiotic from the cell. This is seen in tetracycline and quinolone resistance. Another method is to decrease the cell membrane permeability, which is seen as a bacterial defense in beta-lactam antibiotic and quinolone resistance. In addition, bacteria can prevent influx of the antibiotic by decreasing cytoplasmic membrane transport, as seen with the use of aminoglycosides. Examples of enzymes that deactivate the antibiotic are the lactamases, which deactivate beta-lactams, and the phosphotransferases and acetyltransferases, which deactivate aminoglycosides.

There are numerous methods for altering or bypassing the binding site targeted by the antibiotic. In one method, the target of the antibiotic may be altered in such a way that the antibiotic can no longer bind to and deactivate it. Examples of this method include alterations in the deoxyribonucleic acid (DNA) gyrase that prevent the binding of quinolones, and methylation of ribosomal ribonucleic acid (rRNA) that prevents the binding of macrolides. An example of an adaptation that bypasses a binding site is the ability of some bacteria to use an alternate metabolic route in folate synthesis, avoiding the effects of trimethoprim [3].

These resistances may be acquired through mutations in the genes that encode for the target or affected transport proteins. As the bacterial cells without the adaptive mutations are killed as a result of an antibiotic, the cells that have the mutation continue to replicate, replacing the original population with a resistant one.

These resistances may also be acquired as a result of the transfer of plasmids or transposons and similar agents. These agents are small segments of DNA that are readily exchanged between bacteria. A plasmid that contains a gene for an adaptive mutation can be shared with a large number of nearby bacteria, which may or may not be the same species. In this manner, resistance can quickly spread from species to species [4].

Many strategies have been used in an attempt to circumvent the multiple mechanisms of resistance that have developed in bacteria. Adding beta-lactamase inhibitors to penicillin drugs, chemically altering cephalosporins to create the additional generations of the drugs, and combining sulfa drugs with pyrimethamine, trimethoprim, and erythromycin are examples of these strategies.

In addition, new categories of antibiotics are being created in an attempt to stay ahead of the rapid evolution of bacterial resistance. Linezolid, the first oxazolidinone, is an example of this. Linezolid is a unique drug that prevents formation of the 70S protein synthesis complex in bacteria, and it may be useful in the treatment of vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Nonetheless, development of resistance in bacteria is relentless.

In light of the efficient means by which bacteria develop resistances, it is important to avoid practices that contribute to the process. The Centers for Disease Control and Prevention (CDC) has issued a position paper outlining recommendations for minimizing nosocomial infection and the emergence of resistant organisms [5]. In this paper, the CDC recommended a multistep approach.

The first step recommended by the CDC is to prevent infection. Many infections in hospitalized or institutionalized patients are the direct result of indwelling urinary catheters, central venous catheters, and intubation. These invasive medical devices should be avoided unless they are clearly indicated. In addition, proper vaccination of medical staff and patients is an effective method to prevent the spread of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

The next step is to tailor medical treatment to fit the infection. Antimicrobial therapy should be based on the likely pathogens or culture results, so broad-spectrum antibiotics may be avoided when possible. Consideration should be given to pathogens common to the area of infection (e.g., skin, intra-abdominal) and to pathogens common in the environment locally (e.g., hospital environment). Prolonged treatment regimens may allow more time for the development of resistance, so the duration of therapy must be considered as well.

The last step is to prevent the transmission of resistant bacteria between patients. A simple, effective method of infection containment is hand washing. As noted in the CDC position paper, participation in hospital infection control programs is also necessary [5]. A coordinated effort to contain pathogens within hospital infection control guidelines makes it easier to prevent the spread of multidrug-resistant bacteria.

Despite the remarkable rate of the development of new antibiotics, the emergence of drug-resistant bacteria continues unabated. Therefore, it is important to use antibiotics wisely to maintain their usefulness for the future.



A meta-analysis published by the Cochrane Database of Systematic Reviews found that interventions to improve antibiotic prescribing to hospital inpatients are successful and can reduce antimicrobial resistance or hospital-acquired infections.

(<http://www.cochrane.org/reviews/en/ab003543.html>. Last accessed January 14, 2009.)

Level of Evidence: Meta-analysis

CONSIDERATIONS FOR NON-ENGLISH PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of the appropriate prescription of antibiotics, particularly in empirical treatment. Furthermore, communication with patients regarding treatment regimens and compliance depends on clear communication between the patient and clinician. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. The interpreter should be considered an active agent in the diagnosis and/or treatment processes, negotiating between two cultures and assisting in promoting culturally competent communication and practice [151].

PENICILLINS

Penicillin was discovered by Alexander Fleming in 1928. After observing that *Penicillium* colonies inhibited the growth of staphylococci on agar plates, Fleming made an extract from the mold and proved that it inhibited bacterial growth. Penicillin became available for general use in the 1940s [150].

MECHANISM OF ACTION

Penicillin is bactericidal, killing bacterial cells by impairing cell wall synthesis. It impairs cell wall synthesis by preventing cross-binding of the peptidoglycan polymers necessary for cell wall formation and by binding the penicillin-binding proteins (PBPs) (carboxypeptidases, endopeptidases, and transpeptidases) that participate in cell wall synthesis [6]. Although the exact mechanisms involved are not known, the end result is that the cell wall is structurally weakened and lyses, leading to cell death.

The basic form of penicillin is structured around the beta-lactam ring (a thiazolidine ring) and can be altered by substituting side chains. By doing so, the antimicrobial spectrum, absorption characteristics, and resistance to beta-lactamase deactivation can be altered.

Bacterial resistance to penicillins may take different forms. The most significant is the bacterial production of beta-lactamases, which can destroy the beta-lactam ring by means of hydrolysis, effectively preventing antimicrobial activity by the agent [7]. In addition, some bacteria are able to prevent binding to the PBPs by various means, including altered binding sites for the penicillins [8].

Various strategies have been employed to circumvent these microbial adaptations. Altering the structure of the penicillins to produce agents that are more resistant to the hydrolysis from the beta-lactamases has resulted in the development of the extended-spectrum penicillins.

Another strategy has been to combine penicillins with other agents that either block bacterial beta-lactamases or have an alternate method for killing bacteria that are resistant to penicillin. Examples include amoxicillin plus clavulanic acid, ampicillin plus sulbactam, piperacillin plus tazobactam, and ticarcillin plus clavulanic acid. Clavulanic acid is produced by *Streptomyces clavuligerus*. Sulbactam and tazobactam are derived from the basic penicillin ring. These agents have little intrinsic antimicrobial activity, but they bind irreversibly to many beta-lactamases, preventing hydrolytic activity against the beta-lactam ring.

PHARMACOKINETICS

Penicillins can be separated into groups based on their pharmacokinetics and antibacterial activity. These groups are the natural penicillins, the aminopenicillins, the penicillinase-resistant penicillins, and the antipseudomonal penicillins [9].

THE NATURAL PENICILLINS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Natural Penicillins					
Penicillin G	1.2 MU	25,000-50,000 U/kg in one dose Max: 1.2 MU	IM	Rash, GI upset	Indicated for syphilis and group A strep infections. Intravenous forms of Penicillin G are available.
Penicillin V	250 mg twice daily	<5 yrs: 125 mg twice daily >5 yrs: 250 mg twice daily	PO	Rash, GI upset	Note: IV administration has been associated with cardiorespiratory arrest and deaths.
Aminopenicillins					
Amoxicillin	250-500 mg every 8 hrs or 500-875 mg every 12 hrs	20-40 mg/kg/day divided every 8 hrs or 25-45 mg/kg/day divided every 12 hrs <3 mos: Max: 30 mg/kg/day	PO	Rash, diarrhea	Dosing for amoxicillin/clavulanate is based on the amoxicillin component; the ES formulation of amoxicillin/clavulanate is not interchangeable with the regular suspension.
Ampicillin	PO: 250-500 mg every 6 hrs IV, IM: 250-500 mg every 6 hrs	PO: 50-100 mg/kg/day divided every 6 hrs Max: 2-3 g/day IV, IM: 100-150 mg/kg/day divided every 6 hrs Max: 2-4 g/day	PO IV IM	Rash, GI symptoms (very common)	The IV form can be given in divided doses or in a continuous infusion.
Penicillinase-Resistant Penicillins					
Dicloxacillin	125-250 mg every 6 hrs	<40 kg: 12.5-25 mg/kg/day in 4 divided doses >40 kg: 125-250 mg every 6 hrs	PO	Rash, diarrhea	Not recommended for use in neonates.
Nafcillin	IV: 0.5-2 g every 4 to 6 hrs IM: 0.5 g every 4 to 6 hrs	Neonates: 50 mg/kg/day in 4 divided doses Children: IV: 50-100 mg/kg/day in 4 divided doses IM: 25 mg/kg every 12 hrs	IV IM	Phlebitis at IV site, neutropenia, rash	Tissue necrosis can occur with IV extravasation.
Oxacillin	0.25-1 g every 4 to 6 hrs	100-150 mg/kg/day in 4 divided doses Max: 4 g/day	IV IM	Phlebitis at IV site, hepatitis, rash	The drug-induced hepatitis is usually reversible if drug is discontinued. Neonatal dosing may require the use of alternate container system/dosage forms.

Table 1 continues on next page.

THE NATURAL PENICILLINS (Continued)					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Antipseudomonal Penicillins					
Carbenicillin	1-2 tablets (382-764 mg) every 6 hrs	30-50 mg/kg/day in 4 divided doses Max: 2-3 g/day	PO	Rash, GI upset	Limit to treatment of urinary tract infections; potential warfarin interaction.
Piperacillin	IV, IM: 3-4 g every 4 to 6 hrs Max: 24 g/day	Neonates: IV, IM: 100 mg/kg every 12 hrs Infants/Children: IV, IM: 200-300 mg/kg/day divided every 4 to 6 hrs	IV IM	Rash, GI upset, phlebitis at infusion site	N/A
Ticarcillin	3.1 g every 4 to 6 hrs Max: 24 g/day	<60 kg: 200-300 mg/kg/day divided every 4 to 6 hrs >60 kg: use adult dosing	IV	Rash, GI upset	Potential warfarin interaction. Ticarcillin/clavulanate doses are based on the ticarcillin component.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. MU = million units; GC = gonococcal infection; ES = extra strength.					
Source: [148; 149]					Table 1

The Natural Penicillins

The natural penicillins include penicillin G and penicillin V. Penicillin G is very unstable in stomach acid and must be given parenterally. Penicillin V was developed to be more stable in stomach acid and is given orally.

The natural penicillins are active against gram-positive organisms, such as many staphylococci, many streptococci, *Enterococcus faecalis*, and *Listeria monocytogenes*. They are also active against anaerobic species, such as *Bacteroides* species and *Fusobacterium* species. The natural penicillins are effective against some gram-negative bacteria, such as *Escherichia coli*, *H. influenzae*, *Neisseria gonorrhoeae*, *Treponema pallidum*, and susceptible *Pseudomonas* species, and they are indicated for use in infections caused by penicillin-sensitive organisms. The sensitivity should be proven for moderate-to-severe infections if resistant organisms are likely. Labeled uses include treatments for

infections of the upper and lower respiratory tract, throat, skin, and genitourinary tract [149].

The Aminopenicillins

The aminopenicillins have about the same activity as the natural penicillins, plus improved coverage of gram-negative cocci and *Enterobacteriaceae*. These agents are not active against *Treponema* species or *Actinomyces* species, but amoxicillin/clavulanic acid and ampicillin/sulbactam have better coverage against *H. influenzae* and *Klebsiella* species than the natural penicillins and the aminopenicillins alone.

The aminopenicillins include ampicillin and amoxicillin. Ampicillin can be given parenterally or orally. Amoxicillin was specifically designed to be stable in stomach acid, and its absorption is considerably better than that of ampicillin. Improved absorption also means that amoxicillin causes less diarrhea than other oral penicillins.

The Penicillinase-Resistant Penicillins

The penicillinase-resistant penicillins were developed in response to the discovery of resistant staphylococcal bacteria that could deactivate available penicillins. These penicillins are resistant to hydrolysis by the lactamase produced by the staphylococci, and they include nafcillin and oxacillin, which are parenteral formulations, and dicloxacillin, which is given orally. Methicillin and cloxacillin are no longer available in the U.S.

While the penicillinase-resistant penicillins are effective against many of the same gram-positive organisms that the natural penicillins are effective against, they are not effective against gram-negative or anaerobic organisms. They are, however, notable for their usefulness against penicillin-resistant *Staphylococcus* and *Streptococcus* species.

The Antipseudomonal Penicillins

The antipseudomonal penicillins are often also referred to as extended-spectrum penicillins. These include carbenicillin (oral), and ticarcillin and piperacillin (both of which are parenteral). Mezlocillin, which was also parenteral, is no longer available in the U.S.

These agents retain much of their activity against gram-positive bacteria, but they also have more activity against gram-negative bacteria and are much more active against *Pseudomonas aeruginosa* than ampicillin. Additional gram-negative species that are treated by these agents include *H. influenzae*, *Serratia* species, and *Klebsiella* species. These agents are not active against *T. pallidum* or *Actinomyces* species.

The Addition of Beta-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam increase the spectrum of activity of the drug with which they are compounded. They are generally active against the beta-lactamases produced by *H. influenzae*, *Moraxella catarrhalis*, and *S. aureus*. However, their activity is variable against some of the gram-negative bacteria, such as some species of *Pseudomonas*, *Enterobacter*, *E. coli*, *Klebsiella*, and *Serratia*, due to resistance to these beta-lactamase inhibitors [10].

ABSORPTION/ELIMINATION

While most penicillins can be absorbed orally, the bioavailability varies considerably. Penicillin V, amoxicillin, ampicillin, dicloxacillin, and carbenicillin can be given orally. Food may interfere with absorption with all oral penicillins, except carbenicillin and penicillin V. The remaining penicillins are too unstable in the acidic environment of the stomach and must be given parenterally.

Once absorbed, these agents are widely distributed throughout the body. Therapeutic concentrations of penicillins are readily achieved in tissues and secretions, e.g., joint fluid, pleural fluid, pericardial fluid, and bile. Low concentrations are found in prostatic secretions, brain tissue, intraocular fluid, and phagocytes. Cerebrospinal fluid (CSF) concentrations vary but are less than 1% of serum concentration when the meninges are normal. When the meninges are inflamed, CSF concentrations may rise to 5% and can be increased by co-administration of probenecid [11]. Concentration in urine is high due to renal secretion.

Penicillins are eliminated rapidly by the kidneys as a result of glomerular filtration and renal tubular secretion. Probenecid markedly reduces the tubular secretion of the penicillins and decreases the apparent volume of distribution, resulting in higher serum levels. All of the penicillins are excreted to some degree in the bile, but biliary excretion is most important for antipseudomonal penicillins and nafcillin [12].

In patients with mild renal insufficiency, dosage adjustment is not needed, except with the use of ticarcillin [13]. If the creatinine clearance is less than 10 ml/min, then dosage adjustments should be made to avoid excess serum levels. Nafcillin undergoes extensive hepatic metabolism, and the dosage must be adjusted for severe renal and hepatic insufficiency. Carbenicillin is not recommended in renal failure, as it is not excreted in adequate amounts to reach the bladder [7].

TOXICITIES/SIDE EFFECTS

These drugs are usually well tolerated. However, gastrointestinal (GI) disturbances may occur with all oral penicillins.

Allergy to any of the penicillins is the only absolute contraindication to use of a penicillin agent. Allergic reactions occur in up to 10% of patients, with 0.001% dying from anaphylaxis [14]. The allergic responses vary and can include a mild rash (the most common) and urticaria. Rarely, serum sickness, exfoliative dermatitis, and Stevens-Johnson syndrome may develop [12]. These allergic responses develop in response to the beta-lactam ring and its derivatives; therefore, it should be noted that the penicillins are cross-reactive.

Rarely, penicillins may cause hematologic reactions with neutropenia due to reversible bone marrow suppression. Abnormal platelet aggregation may occur, particularly with carbenicillin and ticarcillin [15]. Other rare reactions include hepatitis, seizures, interstitial nephritis, and hypokalemia due to local effects in the renal tubules.

DRUG INTERACTIONS

The penicillins should not be given concurrently with tetracycline or other bacteriostatic agents. Penicillin works in cells that are actively synthesizing cell wall components, and if metabolism is prevented, then the actions of penicillin may be impaired. The antipseudomonal penicillins also may affect warfarin metabolism. Therefore, the prothrombin time, using the international normalized ratio (INR), should be monitored [16].

SPECIAL POPULATIONS

The penicillins are pregnancy category B, indicating no adverse events noted in animal studies [17]. These agents are secreted in breastmilk, and breastfeeding should be avoided if the infant is allergic to any of the penicillins [18].

CEPHALOSPORINS

The first cephalosporin was discovered in 1948 by Giuseppe Brotzu, who observed that the fungus *Cephalosporium acremonium* produced a substance that inhibited the growth of *S. aureus* and other bacteria. The initial substance was identified and modified to create the cephalosporins that are now used. The cephamycins were created by adding a methoxy group on the beta-lactam ring of the original compound, based on the structure of cefoxitin, produced by *Streptomyces lactamdurans*. By altering the chemical groups substituted on the basic molecule, greater antimicrobial activity and longer half-lives have been obtained [19].

MECHANISM OF ACTION

Like penicillins, the cephalosporins are beta-lactams in which the beta-lactam ring is joined to a dihydrothiazine ring. Their antimicrobial effect is based on the same mechanism of action that occurs in the penicillins. The cephalosporins inhibit bacterial cell wall synthesis by blocking the transpeptidases and other PBPs involved in the synthesis and cross-linking of peptidoglycan [20; 21].

Because each bacterial species has a unique chemical structure in its cell wall, the cephalosporins may have different mechanisms of action by which they inhibit cell wall synthesis.

As with penicillins, resistance to the action of cephalosporins may result from mutations in the penicillin-binding proteins (preventing the cephalosporins from binding to them) and from the production of extended-spectrum beta-lactamases that deactivate the drug [22]. An additional source of resistance in gram-negative bacteria is alteration in the cell-membrane porins that normally allow passage of the cephalosporins [23].

Of these mechanisms, the production of beta-lactamase is the most clinically significant. This form of resistance may occur through mutations or may be carried on plasmids [24].

THE CEPHALOSPORINS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
1st Generation					
Cefadroxil	1-2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	PO	Rash, diarrhea	N/A
Cefazolin	1-2 g every 8 hrs or 0.5-1 g every 6 to 8 hrs Max: 12 g/day	>1 mo: 25-100 mg/kg/day in 3-4 divided doses Max: 6 g/day	IV, IM	Phlebitis at infusion site, rash, diarrhea	N/A
Cephalexin	.25-1 g every 6 hrs Max: 4 g/day	>1 yr: 25-100 mg/kg/day in 3-4 divided doses	PO	GI upset, rash	Can interfere with some urine glucose tests.
Cephradine	250-500 mg every 6 to 12 hrs	>9 mos: 25-50 mg/kg/day in 2-4 divided doses	PO	Rash, GI upset	Parenteral form is no longer available in the U.S. Can interfere with some urine glucose tests.
2nd Generation					
Cefaclor	250-500 mg every 8 hrs	>1 mo: 20-40 mg/kg/day, in 2-3 divided doses Max: 1 g/day	PO	Rash, GI upset	Can interfere with some urine glucose tests.
Cefotetan	1-2 g every 12 hrs	Not studied for pediatric use	IV, IM	Phlebitis at infusion site, rash, GI upset	Disulfiram-like reaction with alcohol. Can interfere with some urine glucose tests.
Cefoxitin	1-2 g every 6 to 8 hrs Max: 12 g/day	>3 mos: 80-100 mg/kg/day in 4-6 divided doses	IV, IM	Phlebitis at infusion site, rash	IM injection is painful. Can interfere with some urine glucose tests.
Cefprozil	250 mg every 12 hrs or 500 mg/day	>6 mos: 7.5-15 mg/kg every 12 hrs >2 yrs: 7.5-15 mg/kg/day in 2 divided doses or 20 mg/kg every 24 hrs Max: 1 g/day	PO	Rash, GI upset, elevated liver enzymes	Avoid use in phenylketonuria. Can interfere with some urine glucose tests.
Cefuroxime	PO: 250-500 mg every 12 hrs IV, IM: .75-1.5 g every 6 to 8 hrs or 100-150 mg/kg/day in 3-4 divided doses Max: 6 g/day	PO: 20-30 mg/kg/day in 2 divided doses IV, IM: 75-150 mg/kg/day in 3 divided doses Max: 6 g/day	PO, IV, IM	Phlebitis at infusion site, rash, GI upset	Higher doses can be used for severe infection.
3rd Generation					
Cefdinir	300 mg every 12 hrs or 600 mg every 24 hrs	14 mg/kg/day in 1-2 doses	PO	Rash, diarrhea	Iron and antacids can reduce absorption. Can interfere with some urine glucose tests.

Table 2 continues on next page.

THE CEPHALOSPORINS (Continued)					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
3rd Generation (Continued)					
Cefditoren pivoxil	200-400 mg every 12 hrs	Not studied for patients <12 yrs of age	PO	GI upset, headache	Interaction with proton-pump inhibitors, H ₂ blockers, antacids. Contraindicated with milk protein allergy.
Cefixime	400 mg/day in 1 or 2 doses	>6 mos: 8-20 mg/kg/day every 12 to 24 hrs Max: 400 mg/day >50 kg or >12 yrs: Use adult dosing.	PO	Diarrhea, rash	Can interfere with some urine glucose tests.
Cefoperazone	1-2 g/day every 12 hrs Max: 12 g/day	100-150 mg/kg/day in 2-3 divided doses Max: 12 g/day	IV, IM	Diarrhea, rash, elevated BUN and serum creatinine	Disulfiram-like interaction with alcohol can occur
Cefotaxime	1-2 g every 4 to 12 hrs	1 mo to 12 yrs (<50 kg): 50-200 mg/kg/day in 3-4 divided doses	IV, IM	Phlebitis at infusion site, rash, GI upset	Single dose can be given for GC. Transient arrhythmias have developed after administration of this agent through central venous catheter.
Cefpodoxime	100-400 mg every 12 hrs	10 mg/kg/day in 2 divided doses Max: 400 mg/day	PO	Diarrhea, nausea, vomiting	Decreased absorption with antacids and H ₂ blockers. Can be given as a single dose for GC.
Ceftazidime	0.5-2 g every 8 to 12 hrs	IV: 30-50 mg/kg every 8 hrs Max: 6 g/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Can interfere with some urine glucose tests. The L-arginine formulation should not be used in children.
Ceftibuten	400 mg every 24 hrs	9 mg/kg/day	PO	Rash, GI upset, headache	N/A
Ceftizoxime	1-4 g every 8 to 12 hrs	150-200 mg/kg in 3-4 doses Max: 12 g/day	IV, IM	GI upset	Transient elevation of liver enzymes may occur in children.
Ceftriaxone	IV: 1-2 g every 12 to 24 hrs IM: 125-250 mg (for GC)	50-100 mg/kg/day in 1-2 divided doses Max: 4 g/day	IV	Phlebitis at infusion site, rash	Avoid in neonates with hyperbilirubinemia. Higher doses are used for meningitis. A ceftriaxone-calcium salt can precipitate in the gallbladder, causing sonographically detectible abnormalities.
4th Generation					
Cefepime	IV: 1-2 g every 8 to 12 hrs IM: 0.5-1 g every 12 hrs	IV, IM: 50 mg/kg every 8 to 12 hrs Not to exceed adult dosing	IV, IM	Phlebitis at infusion site, GI upset	Can interfere with some urine glucose tests.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotics for complete prescribing information, maximum dosages, and indications. GC = gonococcal infection.					
Source: [148; 149]					

Table 2

PHARMACOKINETICS

The cephalosporins have been classified in different ways, based on chemical structure and pharmacologic activities. The most commonly used classification system groups the agents into “generations” based on their similarities in antimicrobial coverage.

First-Generation Cephalosporins

The first-generation cephalosporins are most active against aerobic gram-positive cocci. These agents include cefazolin, cephalexin, cephradine, and cefadroxil, and they are often used for skin infections caused by *S. aureus* and *Streptococcus*. They have activity against *E. coli* and some activity against *H. influenzae* and *Klebsiella* species, but because of the limited gram-negative coverage, they are not first-line agents for infections that are likely to be caused by gram-negative bacteria.

Second-Generation Cephalosporins

The second-generation cephalosporins are more active against gram-negative organisms, such as *Moraxella*, *Neisseria*, *Salmonella*, and *Shigella*. Cefoxitin and cefotetan, which are included in this group under this classification system although they are technically cephamycins, also have more coverage against anaerobic bacteria. The true cephalosporins that are also part of this class are cefprozil, cefuroxime, cefaclor, cefoxitin, and cefotetan. These drugs are used primarily for respiratory tract infections because they are better against some strains of beta-lactamase producing *H. influenzae*.

Third-Generation Cephalosporins

The third-generation cephalosporins have the most activity against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, and *Klebsiella*, while some (ceftazidime) are active against *P. aeruginosa*. These agents have less coverage of the gram-positive cocci, notably methicillin-sensitive *S. aureus*. In addition to the two agents with antipseudomonas coverage, this class includes cefotaxime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, ceftibuten, and cefdinir. These drugs are useful for more severe community-acquired respiratory tract infections, resistant

infections, and nosocomial infections (because of the high incidence of resistant organisms) [25].

Fourth-Generation Cephalosporins

Cefepime is classed as a fourth-generation cephalosporin because it has good activity against both gram-positive and gram-negative bacteria, including *P. aeruginosa* and many *Enterobacteriaceae*. The gram-negative and anaerobic coverage makes cefepime useful for intra-abdominal infections, respiratory tract infections, and skin infections.

ABSORPTION/ELIMINATION

The orally administered cephalosporins include cefaclor, cefadroxil, cephalexin, cephradine, cefprozil, cefuroxime axetil, cefixime, cefpodoxime proxetil, ceftibuten, and cefdinir. In general, the orally administered cephalosporins are absorbed rapidly. Cephalexin, cefadroxil, cefaclor, cefixime, ceftibuten, and cefdinir are nonesterified and are absorbed from the GI tract by active transport in the small intestine. Other agents, such as cefuroxime axetil and cefpodoxime proxetil, are prodrug esters and are passively absorbed. Once absorbed into the cells lining the small intestine, these agents are hydrolyzed and then excreted into the blood stream as active cephalosporins [26].

The presence of food or antacids may increase or decrease the absorption, depending on the drug. Cefuroxime axetil and cefpodoxime proxetil have increased absorption when taken with food. Cefaclor, cefadroxil, cephalexin, and cephradine have slowed absorption when food is in the stomach. Cefixime, cefprozil, and ceftibuten are not affected by the presence of food. Cefpodoxime is the only cephalosporin whose absorption is decreased by the presence of antacids or H₂ antagonists [27].

There is extensive distribution of the cephalosporins into body tissues and fluids. They readily cross the placenta and are also found in synovial fluid. Concentrations in bile and urine are high. Most cephalosporins do not cross into the CSF in sufficient concentration to be recommended for the treatment of meningitis, but there are some exceptions. Cefuroxime, cefotaxime, ceftriaxone, cefepime, and ceftizoxime all have good penetration into the CSF [28].

Most cephalosporins are primarily eliminated by the kidneys. The exception in the oral cephalosporins is cefixime, half of which is excreted in the urine. The remaining half is partly metabolized to inactive metabolites and partly excreted in the bile. Cefotaxime and cephalothin are deacetylated by the liver to a bioactive metabolite and inactive forms. The deacetylated metabolites are then excreted by the kidney. Cepiramide is excreted predominantly in the bile.

In severe hepatic insufficiency, compensatory changes in renal excretion of the hepatically metabolized drugs may occur [29]. However, the dosage of cefotaxime may have to be adjusted. If both severe renal and hepatic insufficiency are present, dosage adjustments of both cefotaxime and ceftriaxone is necessary.

TOXICITIES/SIDE EFFECTS

As a group, cephalosporins are relatively well tolerated [30]. The most common complaints are GI upset, resulting in nausea, vomiting, or diarrhea. Thrombophlebitis can occur with intravenous (IV) administration. One to three percent of patients develop an allergic reaction. Rash, fever, eosinophilia, and urticaria can develop. Anaphylaxis is rare.

Nephrotoxicity may develop [31]. Neurotoxicity is rare. Cephalosporins that contain the methylthiotetrazole (MTT) side chain (cefotetan) may induce a disulfiram-like reaction with alcohol ingestion, e.g., flushing, tachycardia, nausea and vomiting, diaphoresis, dyspnea, hypotension, and confusion. This is due to increased circulating acetaldehyde.

Ceftriaxone has been associated with cholelithiasis due to precipitation in the bile [32].

Rare reactions include hematologic toxicity with resultant eosinophilia, thrombocytopenia, and leukopenia, all of which resolve after stopping treatment [33]. Rarely, hemolytic anemia develops [34]. Hypoprothrombinemia may occur with cephalosporins with the MTT side chain as a result of interference by the MTT moiety with the synthesis of vitamin-K-dependent clotting factors [35].

For patients at high risk of bleeding, exogenous vitamin K may help alleviate this side effect.

False-positive glucosuria testing with a copper reduction test (Clinitest) may occur with cefaclor, cefadroxil, cefotaxime, cefoxitin, and ceftazidime [36].

There is some cross-sensitivity with penicillin allergy, but it is thought to be low in frequency [13]. If a patient develops urticaria, anaphylaxis, or angioedema with penicillins or a cephalosporin, avoid using any of the other cephalosporins.

DRUG INTERACTIONS

The serum levels of all the cephalosporins are increased with co-administration of probenecid. The effects of warfarin may be enhanced by co-administration of cefotetan, cefazolin, cefoxitin, and ceftriaxone. Gentamicin may enhance the nephrotoxic risk of cephalothin.

SPECIAL POPULATIONS

Cephalosporins are generally considered safe to use in pregnancy and are designated as category B. They are excreted in breastmilk in low concentrations, and the American Academy of Pediatrics (AAP) considers this compatible with breastfeeding [37; 38].

CARBAPENEMS

Meropenem, imipenem/cilastatin, doripenem, and ertapenem are parenteral synthetic beta-lactams derivatived from thienamycin, an antibiotic produced by *Streptomyces cattleya* [39]. They have a lactam ring, like the penicillins and cephalosporins, but have a methylene moiety in the ring.

MECHANISM OF ACTION

Like other beta-lactams, the carbapenems inhibit mucopeptide synthesis in the bacterial cell wall by binding to PBPs, leading to lysis and cell death. Bacterial resistance may occur due to a specific beta-lactamase that affects carbapenems. Another significant source of resistance is a mutation that results in the absence of the outer membrane porin, thus allowing transport of the drug into the

cell [40]. Cross-resistance may occur between the carbapenems.

PHARMACOKINETICS

Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against anaerobic bacteria, including *Bacteroides* species. They also cover many gram-positive cocci, such as *Enterococcus* and *Streptococcus*, as well as many gram-negative bacteria [41]. Meropenem has somewhat greater activity against gram-negative bacteria, which are not affected by most beta-lactamases. Doripenem has good activity against *Pseudomonas aeruginosa*.

Imipenem and ertapenem are indicated by the U.S. Food and Drug Administration (FDA) for use in urinary tract infections, pneumonia, intra-abdominal infections, and skin and soft tissue infections [149]. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age [149].

ABSORPTION/ELIMINATION

Imipenem/cilastatin, meropenem, and ertapenem are given parenterally, as they are unstable in stomach acid. Imipenem is combined with cilastatin, which inhibits dehydropeptidase I in the proximal renal tubular cells. Dehydropeptidase I inactivates imipenem by hydrolyzing the beta-lactam ring, so adding the cilastatin allows increased levels of imipenem in the urine and also prevents the production of the nephrotoxic metabolites of imipenem [42]. Meropenem, doripenem, and ertapenem do not require a dehydropeptidase I inhibitor.

Meropenem is well distributed in body tissues and fluids, including the CSF. Imipenem/cilastatin and ertapenem are distributed throughout body tissues, but with only low concentrations in the CSF [43].

Most of the imipenem/cilastatin dose is excreted in the urine. The remaining 20% to 25% of the dose is excreted through an unknown mechanism. Meropenem is excreted unchanged into the urine by means of glomerular filtration and tubular secre-

tion [44]. Ertapenem is metabolized by hydrolysis of the beta-lactam ring, and then both the metabolite and parent drug are excreted in the urine.

The carbapenems require dosage adjustment in patients with renal insufficiency. No changes in dosage are necessary for patients with hepatic insufficiency.

TOXICITIES/SIDE EFFECTS

The carbapenems are generally well tolerated. Occasional reactions include nausea and vomiting, phlebitis at the infusion site, elevation of liver enzymes, and leukopenia. Seizures may occur. The risk is higher in patients with underlying central nervous system (CNS) disease and in patients with renal disease, which results in high serum levels of the drug [45]. Hypersensitivity reactions may occur, and there is a high degree of cross-sensitivity with penicillins. Carbapenems are contraindicated in patients allergic to the carbapenems or penicillins.

DRUG INTERACTIONS

There are few drug interactions associated with the carbapenems, but probenecid may increase the serum levels of meropenem, ertapenem, and imipenem/cilastatin and should be avoided. Ertapenem cannot be infused with dextrose or other medications. Meropenem may reduce levels of valproic acid [46].

SPECIAL POPULATIONS

Meropenem, doripenem, and ertapenem are pregnancy category B, with animal studies showing no adverse reactions [47]. Imipenem/cilastatin is pregnancy category C, based on studies in monkeys that showed increased embryonic loss and side effects in the mother [48]. No data is available regarding breastfeeding and carbapenem administration.

The safety of imipenem and ertapenem use has not been studied in children. Meropenem has been used in children and is indicated by the FDA for the treatment of pediatric meningitis but has not been studied in infants younger than 3 months of age [49].

THE OTHER BETA-LACTAMS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Carbapenems					
Doripenem	1.5 g/day in 3 divided doses	Not studied for children	IV	Headache, rash, nausea, vomiting, diarrhea, phlebitis	Dosage adjustment necessary for renal impairment. Cannot be used in patients with known hypersensitivity to any beta-lactam antibiotic. Seizure risk in patients with CNS disorders.
Ertapenem	1 g/day	15 mg/kg every 12 hrs Max: 1 g/day	IV, IM	Diarrhea, nausea, phlebitis at infusion site	Seizure risk in patients with CNS disorders
Imipenem/cilastatin	IV: 250-1000 mg every 6 to 8 hrs Max: 4 g/day IM: 500-750 mg every 12 hrs Max: 1500 mg/day	<1 wk: 25 mg/kg IV every 12 hrs 1 to 4 wks: 25 mg/kg IV every 8 hrs 4 wks to 3 mos: 25 mg/kg IV every 6 hrs >3 mos: 15-25 mg/kg IV every 6 hrs Max: 2 g/day (for susceptible infections) or 4 g/day (for moderately susceptible infections)	IV, IM	Phlebitis at infusion site, rash	Cross-allergy with penicillin allergy is common. Seizure risk in patients with CNS disorders. Use manufacturer's dosing chart for adults <70 kg.
Meropenem	1.5-6 g/day in 3 divided doses	30-120 mg/kg/day in 3 divided doses Max: 6 g/day	IV	Diarrhea, nausea, inflammation at the injection site, headache	Can cause elevated LFTs. Seizure risk in patients with CNS disorders.
Monobactams					
Aztreonam	IV: 0.5-1 g every 8 to 12 hrs IM: 0.5-2 g every 8 to 12 hrs	30 mg/kg every 6 to 8 hrs Max: 120 mg/kg/day	IV, IM	Rash, nausea, vomiting, phlebitis at infusion site	Rare cross-sensitivity with allergy to other beta-lactams.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. CNS = central nervous system; LFTs = liver function tests (liver enzymes).					
Source: [148; 149]					Table 3

MONOBACTAMS

Monobactams have a single beta-lactam core, distinguishing them from the other beta-lactam drugs [50]. Aztreonam is the only available example of this class of drugs. Aztreonam was originally extracted from *Chromobacterium violaceum*. It is now manufactured as a synthetic antibiotic.

MECHANISM OF ACTION

As with other beta-lactams, aztreonam inhibits mucopeptide synthesis in the bacterial cell wall by binding to the penicillin-binding proteins of gram-negative bacteria, leading to cell lysis and death. Aztreonam is resistant to most beta-lactamases. Treatment in combination with an aminoglycoside appears to be synergistic against *Pseudomonas*.

PHARMACOKINETICS

Aztreonam does not have significant activity against gram-positive or anaerobic bacteria and is primarily used against gram-negative aerobic bacteria, including *P. aeruginosa* and *Klebsiella*. It is indicated for use in pneumonia, soft-tissue infections, urinary tract infections, and intra-abdominal and pelvic infections that are caused by gram-negative aerobic bacteria.

Aztreonam is absorbed rapidly after intramuscular (IM) dosing, but it cannot be given orally due to instability in stomach acid. It is distributed widely in body tissues and fluids, including inflamed meningeal tissue [51]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [52]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [53].

TOXICITIES/SIDE EFFECTS

Frequent adverse reactions include elevations of liver enzymes and transient eosinophilia. Less common reactions include phlebitis at the infusion site, rash, diarrhea, and nausea [54].

There have been a few reports of cross-allergy reactions in patients who are allergic to ceftazidime, but patients with penicillin and cephalosporin allergy can usually tolerate aztreonam [55]. Aztreonam is contraindicated in patients with prior allergic reactions to it or to any component of the formulation.

DRUG INTERACTIONS

No drug interactions have been reported with aztreonam [56].

SPECIAL POPULATIONS

Aztreonam is pregnancy category B, based on animal studies that have shown no ill effects of the drug. There is no human data available [57].

Aztreonam is secreted in breastmilk in low concentrations; breastfeeding is not recommended because the effects of the drug have not been studied in young infants.

Aztreonam has not been studied for use in children younger than 9 months of age but appears safe in children older than 9 months of age. It has been shown to be very useful in children with cystic fibrosis [58].

AMINOGLYCOSIDES

The aminoglycosides were developed during the 1940s. Actinomycetes were studied for possible antimicrobial by-products, and it was found that *Micromonospora* and *Streptomyces* produced useful agents. Streptomycin is derived from *Streptomyces griseus* and was the first of the aminoglycosides that was developed.

MECHANISM OF ACTION

The basic structure of the aminoglycosides is an aminocyclitol ring. Different members of the family have different glycosidic linkages and side groups.

The aminoglycosides have at least two effects on the bacterial cell that ultimately result in cell death. These agents bind negative charges in the outer phospholipid membrane, displacing the cations that link the phospholipids together. This leads to disruption in the wall and leakage of cell contents. In addition, they inhibit protein synthesis by binding to the 30S subunit of the ribosome, causing miscoding and termination [59].

Although resistance to aminoglycosides is less common than with many other antibiotics, it can develop as a result of three known mechanisms. The most common pattern of resistance is through modification of the aminoglycoside molecule itself by enzymes produced by some bacteria. After the aminoglycoside is altered, it cannot bind as well to the ribosomes. The genes that encode for these enzymes are carried on plasmids, allowing rapid transfer of resistance between bacteria. Of note, amikacin has an S-4 amino 2-hydroxybutyryl (AHB) side chain that protects it against deactivation by many bacterial enzymes and is therefore less susceptible to this bacterial defense mechanism [60].

The binding site for aminoglycosides on the rRNA of the ribosome may also be altered, reducing binding. In addition, mutations that cause reduced uptake of aminoglycosides have been documented [60].

To combat resistances and overcome the relative natural resistance of enterococcus to aminoglycosides, other agents that target the cell wall are often used in conjunction with the aminoglycosides. Damage to the cell wall from the additional agents may be bactericidal in some cases and also makes the cell wall more permeable to the aminoglycosides [61].

PHARMACOKINETICS

The aminoglycosides are effective for the treatment of aerobic gram-negative bacilli, such as *Klebsiella* species, *Enterobacter*, and *P. aeruginosa*. There is very little activity against anaerobes and gram-positive organisms, so combination therapy with a penicillin, vancomycin, or other agents against gram-positive organisms and anaerobes is commonly used. The aminoglycosides are indicated for infections caused by susceptible organisms of the urinary tract, respiratory tract, skin and soft tissues, and sepsis due to gram-negative aerobic bacilli.

Aminoglycosides have poor oral absorption, but they are rapidly absorbed after parenteral administration. Neomycin is taken orally as a bowel decontaminant and has minimal absorption. Available parenteral aminoglycosides include amikacin, gentamicin, kanamycin, streptomycin, and tobramycin. They may also be administered directly into intrapleural and intraperitoneal fluid, with rapid absorption. Tobramycin is used for pulmonary infections in cystic fibrosis but must be administered as an inhaled solution to obtain adequate local drug levels [58].

The aminoglycosides are widely distributed in extracellular fluid, including pleural fluid, synovial fluid, abscesses, and peritoneal fluid. They are relatively insoluble in lipid, so the volume of distribution is lower in obese patients. They have poor distribution in bile, aqueous humor, bronchial secretions, sputum, and the CSF [9].

THE AMINOGLYCOSIDES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Amikacin	5-7.5 mg/kg/day in 3 divided doses	5-7.5 mg/kg every 8 hrs	IV, IM	Renal failure, vestibular nerve damage, auditory nerve damage	Predisposition to auditory/vestibular nerve damage may be genetic; check family history. Check serum levels. Doses are based on lean body mass; maintenance dose is based on calculation with creatinine clearance. Additional dose adjustments are needed in renal failure.
Gentamicin	1-2.5 mg/kg every 8 to 12 hrs	<5 yrs: 2.5 mg/kg every 8 hrs >5 yrs: 2-2.5 mg/kg every 8 hrs	IV, IM		
Kanamycin	5-7.5 mg/kg every 8 to 12 hrs Max: 1.5 g/day	15 mg/kg/day in 2-3 divided doses	IV, IM		
Neomycin	500-2000 mg every 6 to 8 hrs or 4-12 g/day in 4-6 divided doses	50-100 mg/kg/day in 3-4 divided doses	PO, topical	Systemic absorption is possible, resulting in the same side effects as amikacin.	Used as a bowel prep for surgery. Is also formulated in some topical eye, ear, and skin preparations.
Streptomycin	15-30 mg/kg/day or 1-2 g/day	20-40 mg/kg/day Max: 1 g/day	IM	Renal failure, vestibular nerve damage, auditory nerve damage	This is the most ototoxic of aminoglycosides; levels must be monitored closely.
Tobramycin	1-2.5 mg/kg every 8 to 12 hrs	<5 yrs: 2.5 mg/kg every 8 hrs >5 yrs: 2-2.5 mg/kg every 8 hrs	IV, IM inhalation solution, ophthalmic drops	Renal failure, vestibular nerve damage, auditory nerve damage	Effects of nondepolarizing muscle relaxants can be increased.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.					
Source: [148; 149]					Table 4

Aminoglycosides are excreted, unmetabolized, by the kidneys. There is no reduction of dosage necessary in liver failure, as there is no hepatic metabolism of these agents. In renal failure, the dosage must be carefully adjusted based on glomerular filtration rate and measured serum levels. Serum levels should be followed in all patients with reduced renal function [63].

TOXICITIES/SIDE EFFECTS

Common side effects associated with aminoglycosides include renal failure that is usually reversible when the drug is discontinued. The exact mechanism of renal injury and how that injury results in decreased glomerular filtration is unknown [64]. It appears that, although there is no hepatic metabolism of the aminoglycosides, concomitant liver disease increases the likelihood of the development of nephrotoxicity [65].

Less commonly, vestibular and auditory impairment may develop during treatment with aminoglycosides. These effects are usually reversible, and because there is some data suggesting that there is a genetic predisposition to this side effect, it should be avoided in patients who have a family history of ototoxicity with aminoglycosides [66].

Streptomycin is the most ototoxic of the aminoglycosides, and levels must be monitored carefully. Neomycin is too ototoxic to use parenterally, so it is used orally to decontaminate the bowel in the treatment of hepatic encephalopathy and in combination therapy to prepare the bowel for surgery.

Neuromuscular blockage has also been observed as a side effect. Aminoglycosides may aggravate muscle weakness in patients with neuromuscular disorders, such as myasthenia gravis and Parkinson's disease, due to a curare-like effect on neuromuscular function [67].

Hypersensitivity reactions are not common with aminoglycosides, but rash, fever, urticaria, angio-neurotic edema, and eosinophilia may occur. Very rare reactions include optic nerve dysfunction, peripheral neuritis, arachnoiditis, encephalopathy, pancytopenia, exfoliative dermatitis, and amblyopia. Bronchospasm and hoarseness have been known to occur with tobramycin inhalation solution [62].

The aminoglycosides are contraindicated in patients with hypersensitivity to the drug. Cross-sensitivity between aminoglycosides does occur. Streptomycin also contains metabisulfite and should be avoided if the patient is allergic to sulfites (more common in asthmatics) [68].

DRUG INTERACTIONS

There are numerous drug interactions that should be taken into consideration when using the aminoglycosides. Nephrotoxicity may be increased with co-administration with other drugs that are nephrotoxic. Loop diuretics (e.g., furosemide) and other ototoxic drugs may increase the incidence of ototoxicity. Respiratory depression may occur if aminoglycosides are given with nondepolarizing muscle relaxants. Neomycin may affect digoxin levels by altering the bowel flora that are responsible for the metabolism of digoxin in the GI tract. Gentamicin may also cause increased serum digoxin levels [69].

In vitro deactivation of penicillins due to acylation has been observed, so the drugs should not be mixed in vitro. Tobramycin inhalation solution cannot be mixed in the nebulizer with dornase alfa [70].

SPECIAL POPULATIONS

Amikacin, streptomycin, tobramycin, and kanamycin are pregnancy category D due to eighth cranial nerve toxicity that has occurred in the fetus with some aminoglycosides. Gentamicin is pregnancy category C due to animal studies that show dose-related nephrotoxicity. Ototoxicity has not been reported with gentamicin, but it may occur. Neomycin is pregnancy category C due to minimal systemic absorption of the oral dose. Despite these categorizations by the manufacturers, some authorities think that these agents may be used if the benefit outweighs the potential risk [71].

Traces of aminoglycosides are excreted in breastmilk, but the AAP considers this compatible with breastfeeding because aminoglycosides are very poorly absorbed from the GI tract [38]. However, they may cause alterations in the normal bowel flora of the infant.

Half-life alterations occur in patients at extremes of age. The half-life in neonates and low-birth-weight infants may be considerably prolonged. The elderly may also have a longer aminoglycoside half-life due to an age-related decrease in renal function [62].

MACROLIDES AND TELITHROMYCIN

The original macrolide, erythromycin, was discovered in 1952 by J.M. McGuire. It is produced by *Saccharopolyspora erythrae* (formerly known as *Streptomyces erythreus*). Semisynthetic derivatives (clarithromycin, azithromycin) have been produced from the original erythromycin, with modifications that improve acid stability, antibacterial spectrum, and tissue penetration.

MECHANISM OF ACTION

The macrolides are bacteriostatic, inhibiting protein synthesis by binding at the 50S ribosomal unit and by blocking transpeptidation and translocation. At high concentrations or with rapid bacterial growth, the effects may be bactericidal [72].

Telithromycin is technically a ketolide, but it is structurally related to the macrolides. It also functions by binding the ribosomal subunit with subsequent inhibition of bacterial protein synthesis. By binding in two places, telithromycin remains active against bacteria that produce methylases, which alter binding at the domain V site on the ribosomal subunit [73].

Many bacteria that are resistant to the penicillins are also resistant to erythromycin. Bacterial resistance may result from decreased permeability of the cell membrane; in addition, an increase in active efflux of the drug may occur by incorporating a transporter protein into the cell wall [74]. The gene for this mechanism is transferred on plasmids between bacteria. Mutations of the 50S ribosomal receptor site may also develop, preventing binding of the erythromycin. Lastly, bacterial enzymes have been described that may deactivate erythromycin [75]. It is likely that this form of resistance is also transferred on plasmids.

Many strains of *H. influenzae* are resistant to erythromycin alone but are susceptible to a combination with a sulfonamide [76]. Erythromycin ethylsuccinate and sulfoxazole are manufactured as suspensions for use in treating acute otitis media in children older than 2 months of age. They are useful for targeting *H. influenzae*, one of the common pathogens in otitis media in this age group.

PHARMACOKINETICS

Erythromycin has a wide spectrum of activity. Gram-positive bacteria that are usually susceptible to erythromycin include the *Streptococcus* species. Erythromycin is a second-line agent for gram-negative bacteria, such as *H. influenzae* and *M. catarrhalis*. Macrolides are particularly useful for their coverage of atypical bacteria, such as *Mycoplasma* and *Chlamydia*. Some spirochetes and mycobacteria are also susceptible to the macrolides. These drugs are indicated for upper respiratory tract infections, such as sinusitis, otitis media, pharyngitis, and bronchitis. They are also useful in the treatment of pertussis, Legionnaires' disease, and diphtheria. Telithromycin is indicated for community-acquired pneumonia [149].

Erythromycin base is deactivated by gastric acid, so it is formulated in enteric-coated tablets or capsules that protect the drug until it reaches the duodenum, where it is absorbed. Eating increases stomach acid secretion and may slow absorption as a result. The ester forms of the erythromycin base (stearate, estolate, and ethylsuccinate) were all formulated to improve absorption. The estolate is the best absorbed of the three after eating; the ethylsuccinate form is best absorbed in the fasting state [77]. Erythromycin may also be given intravenously.

Clarithromycin and azithromycin have excellent absorption after oral dosing. Clarithromycin and telithromycin may be given with food, but for azithromycin, the presence of food in the stomach causes significant delays in absorption [78].

THE MACROLIDES AND TELITHROMYCIN					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Macrolides					
Azithromycin	PO: 250-600 mg/day or 1-2 g/day IV: 250-500 mg/day	PO: 5-12 mg/kg/day Max: 500 mg/day or 30 mg/kg as single dose Max: 1500 mg/day	PO, IV	GI upset	One dose of 1 g given PO can be used for non-GC urethritis/cervicitis. Interaction with pimozide/cyclosporine.
Clarithromycin*	250-500 mg every 12 hrs or 1 g/day extended-release formulation	7.5 mg/kg every 12 hrs	PO	GI upset, metallic taste	Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions. Special dosing combined with omeprazole and amoxicillin is one regimen used for <i>H. pylori</i> treatment.
Erythromycin	Base: 250-500 mg PO every 6 to 12 hrs Max: 4 g/day Ethylsuccinate: 400-800 mg PO every 6 to 12 hrs Max: 4 g/day Lactobionate: 15-20 mg/kg/day IV in 4 divided doses or 0.5-1 g IV every 6 hrs Continuous infusion over 24 hrs possible. Max: 4 g/day	Base: 30-50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Ethylsuccinate: 30-50 mg/kg/day PO in 2 to 4 divided doses Max: 3.2 g/day Stearate: 30-50 mg/kg/day PO in 2 to 4 divided doses Max: 2 g/day Lactobionate: 15-50 mg/kg/day IV in 4 divided doses Max: 4 g/day	PO, IV, topical ophthalmic solution	GI intolerance (common), phlebitis at IV infusion site	Inhibits liver CYP 450 enzymes 3A4 and 1A2, resulting in multiple significant drug interactions.
Ketolides					
Telithromycin	800 mg every 24 hrs	Not studied for children <13 yrs of age >13 yrs: Use adult dosing	PO	Nausea, diarrhea	Occasionally causes visual changes (reversible). Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions.
<p>Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.</p> <p>Non-GC = nongonococcal infection.</p> <p>*In December 2005, the U.S. Food and Drug Administration (FDA) issued an alert for this drug.</p>					
Source: [148; 149]					

Table 5

All the macrolides have extensive tissue distribution, with less than adequate penetration into the brain tissue and the CSF [79]. Erythromycin and azithromycin are primarily excreted unchanged into the bile. Clarithromycin is excreted in the bile and in the urine, both unchanged and as the hydroxy metabolite. Telithromycin undergoes hepatic metabolism and is eliminated mainly in the bile, but also in the urine [80].

It may be necessary to adjust the doses of the macrolides in the presence of severe hepatic insufficiency. Azithromycin and clarithromycin doses may have to be reduced in severe renal failure. Because telithromycin is eliminated by more than one mechanism, hepatic or renal insufficiency is unlikely to affect serum levels unless they are both present [81].

TOXICITIES/SIDE EFFECTS

While serious side effects with the macrolides are rare, milder side effects are common. Erythromycin stimulates motility in the GI tract, and this may cause abdominal cramping, diarrhea, nausea, and vomiting. Hepatic dysfunction with or without jaundice has occasionally been reported. There have also been some reports of reversible hearing loss in patients treated with erythromycin in high doses or in the presence of renal insufficiency. With IV erythromycin, prolongation of the QT interval and ventricular tachycardia may occur [82].

Clarithromycin may cause nausea, diarrhea, abnormal taste, dyspepsia, and headache. There have been reports of tooth discoloration that is reversible with professional cleaning. Transient CNS changes with anxiety and behavioral changes, which resolve when the drug is discontinued, have also been reported [83].

Side effects from telithromycin include nausea and diarrhea in up to 10% of treated patients [84]. Occasional side effects include headache, dizziness, vomiting, reversible liver function test (LFT) elevation, and hepatitis. Reversible vision blurring and diplopia occurs in 1% of patients [84]. Exacerbations of myasthenia gravis have been reported as well. QT interval elongation may occur, so telithromycin should be avoided in patients at risk for arrhythmias [84].

Allergic reactions to macrolides are rare, but may include rash and eosinophilia. Very rarely, severe reactions such as Stevens-Johnson syndrome have occurred. The drugs are contraindicated in patients with known hypersensitivity to the macrolides.

DRUG INTERACTIONS

Drug interactions are extensive. Erythromycin and clarithromycin are inhibitors and substrate for the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A4). If they are given with a drug that is primarily metabolized by CYP3A, the drug serum levels may be increased and/or prolonged [85]. Erythromycin and clarithromycin are contraindicated with concurrent use of cisapride, pimozone, astemizole, or terfenadine. Serum levels of theophylline, cyclosporine, digoxin, ergotamine, carbamazepine, benzodiazepines, warfarin, amiodarone, and tacrolimus may also be affected by concurrent administration with erythromycin and clarithromycin. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors levels may also be elevated, with increased risk for rhabdomyolysis [86].

Azithromycin is not likely to interact with drugs metabolized by CYP3A4. However, azithromycin interacts with pimozone, potentially resulting in QT interval prolongation and arrhythmia [87]. In addition, cyclosporin levels may be altered [88].

Co-administration of pimozone is contraindicated. Levels of cyclosporine could potentially be increased and therefore should be monitored closely [88].

Telithromycin is metabolized in the liver, partly by the P450 enzyme system and partly by other mechanisms. It may interact with the following drugs: cisapride, pimozide, quinidine, procainamide, dofetilide, rifampin, ergot alkaloids, itraconazole, ketoconazole, midazolam, digoxin, cyclosporine, carbamazepine, hexobarbital, phenytoin, tacrolimus, sirolimus, metoprolol, theophylline, and statins. Telithromycin is contraindicated in patients allergic to macrolides or telithromycin. It should not be given with cisapride or pimozide [84]. An interaction between warfarin and telithromycin has also been reported [89].

SPECIAL POPULATIONS

Erythromycin is pregnancy category B, with an erythromycin estolate preparation as the preferred form because it is less likely to cause hepatotoxicity. Surveillance studies have not shown any increase in adverse outcomes. The CDC recommends the use of erythromycin for the treatment of *Chlamydia* during pregnancy [90]. Azithromycin is also category B, based on animal studies. It has been used safely to treat *Chlamydia* in pregnant women [91].

Clarithromycin is pregnancy category C, based on the finding that it causes growth retardation in monkeys and adverse effects on other mammals. A postmarketing surveillance study did not find any evidence of teratogenicity, but another study found a higher rate of spontaneous abortion in those treated with clarithromycin [92; 93].

Erythromycin is excreted in breastmilk, but the AAP considers it usually compatible with breastfeeding [38]. Clarithromycin is excreted in breastmilk in lactating animals, but the effects have not been studied in humans. There have been some reports of infantile hypertrophic pyloric stenosis following treatment of newborns with erythromycin [94].

QUINOLONES

The first quinolone, nalidixic acid, was introduced in 1962. It was developed as a result of chloroquine synthesis. Later, derivatives with broader spectrum antimicrobial coverage were produced, leading to the current class of quinolone drugs. As with other classes of synthetic and semisynthetic antimicrobials, alterations of side chains affect antimicrobial activity and pharmacokinetics [95].

MECHANISM OF ACTION

Quinolones cause bacterial cell death by inhibiting DNA synthesis. They inhibit DNA gyrase and DNA topoisomerase, enzymes that mediate DNA supercoiling, transcription, and repair [96]. The exact mechanism by which this leads to cell death has not yet been determined.

Bacterial resistance develops as a result of spontaneous mutations that change the binding sites for quinolones on the DNA gyrase and the DNA topoisomerase [97]. Mutations that decrease the ability of quinolones to cross the cell membrane also occur. Some of these resistances may be transferred from other bacteria by means of plasmids [98].

PHARMACOKINETICS

The quinolones are active against many gram-negative cocci, gram-negative bacilli, atypical bacteria (e.g., *Legionella*, *Mycoplasma*), and staphylococci. Activity against streptococci and anaerobes is not as strong, although newer agents, such as moxifloxacin, have better coverage for these [99]. Gram-negative coverage includes *Campylobacter*, *Enterobacter*, *E. coli*, *H. influenzae*, *Klebsiella*, *Salmonella typhi*, *Shigella*, and *Vibrio cholerae*. Indications for the use of quinolones include urinary tract infections, *N. gonorrhoeae* infections of the urethra and cervix, pneumonia, sinusitis, soft tissue infections, and prostatitis. Ciprofloxacin is indicated for post-exposure prophylaxis for anthrax, and levofloxacin has an indication for the treatment of inhalation anthrax infection. The quinolones are absorbed well from the GI tract. Food may delay the time

to reach peak serum concentration but does not decrease total absorption. The drugs are distributed well throughout all tissues, including the prostate, although the levels in the CSF and prostatic fluid are lower than serum levels [100].

Clearance mechanisms vary between the quinolones. Levofloxacin and ofloxacin are mainly cleared by renal excretion and have minimal hepatic clearance [101]. Moxifloxacin is mainly excreted nonrenally. Moxifloxacin is metabolized, via glucuronide and sulfate conjugation in the liver, to an inactive metabolite [102].

Norfloxacin, ciprofloxacin, and gemifloxacin have mixed routes of elimination. Norfloxacin has some hepatic metabolism to active metabolites; the metabolites and parent drug are excreted by the kidney. About 30% of the dose of norfloxacin is excreted in the stool, in the bile, and as unabsorbed drug. As much as 50% of the ciprofloxacin dose is excreted renally, and 40% is excreted in the bile after hepatic metabolism. Approximately 60% of gemifloxacin is excreted in the feces, and the remainder is excreted in the urine.

In renal insufficiency, the quinolones that are primarily excreted renally and those with mixed routes of elimination require dosage adjustments [103]. Moxifloxacin doses do not have to be adjusted for mild hepatic insufficiency, although this has not been studied in severe hepatic insufficiency [102].

TOXICITIES/SIDE EFFECTS

The most common side effect with the use of quinolones is GI upset. Less common side effects include headache, insomnia, dizziness, peripheral neuropathy, tendon rupture, elevated liver enzymes, and interstitial nephritis [104; 105]. Rarely, hematologic toxicities have occurred, resulting in hemolytic anemia (more likely to occur in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency), aplastic anemia, and agranulocytosis [106]. Very rarely, hepatic necrosis and hepatic failure have been reported [107].

Although allergic reactions are not common, they may occur and range from a rash to severe reactions, such as Stevens-Johnson syndrome. Very rare cases of severe fatal hypoglycemia have been reported with concurrent treatment with glyburide and ciprofloxacin [108]. Use quinolones with caution in patients with medical problems that predispose the patient to seizures.

DRUG INTERACTIONS

Drug interactions are common and vary among the quinolones. Antacids may decrease the absorption of these agents. Iron supplements and other supplements with divalent and trivalent cations cause quinolone-cation complexes and impair absorption [109]. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) appear to increase the risk of seizures [110].

Theophylline, phenytoin, warfarin, and mexiletine levels may be elevated in patients concurrently treated with ciprofloxacin. Serum levels or prothrombin time should be monitored, and the doses of these drugs should be altered as appropriate. Dosage adjustments are not typically needed with other quinolones [111].

SPECIAL POPULATIONS

Quinolones are not recommended during pregnancy. Animal studies have demonstrated arthropathy in immature animals [112]. It is presumed that quinolones are excreted in breastmilk, and due to the risk for arthropathy, breastfeeding while taking a quinolone should be avoided.

It is unclear if these effects cause clinically significant changes in humans, so there is debate over whether it is safe to use the drugs in children [113]. Quinolones have been used in pediatric patients with cystic fibrosis, but they should only be used in patients younger than 18 years of age if the benefits outweigh the risks [114].

THE QUINOLONES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Ciprofloxacin	PO: 250-750 mg every 12 hrs IV: 400 mg every 12 hrs	PO: 20-30 mg/kg/day in 2 divided doses Max: 1.5 g/day IV: 20-30 mg/kg/day in 2 divided doses Max: 800 mg/day	PO, IV, topical, otic, ophthalmic	GI upset, headache	Photosensitivity can occur. Antacids decrease absorption. Can prolong QT interval.
Gemifloxacin	320 mg/day	N/A	PO	GI upset, headache, rash	
Levofloxacin	250-500 mg/day	N/A	PO, IV, topical	GI upset, headache, phototoxicity	
Lomefloxacin	400 mg/day	N/A	PO	GI upset, headache	
Moxifloxacin	400 mg/day	N/A	PO, IV, topical, ophthalmic	GI upset, headache	
Gatifloxacin	1 drop per eye every 2 hrs Max: 8 drops/day	See adult dosing	Ophthalmic	Conjunctival irritation, keratitis	
Norfloxacin	400 mg every 12 hrs or 800 mg as a single dose for GC*	N/A	PO, ophthalmic	GI upset, headache	Antacids decrease absorption.
Ofloxacin	200-400 mg every 12 hrs	N/A	PO, IV, otic, ophthalmic		
<p>Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications.</p> <p>GC = gonococcal infection.</p> <p>*As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of uncomplicated gonococcal disease.</p>					
Source: [148; 149]					Table 6

SULFONAMIDES

Sulfonamides, the first true antibiotics, are derived from azo dyes. The first agent was sulfachrysoidine, used in 1935, which released sulfanilamide in vivo [115]. Modifications were made to the sulfanilamide to reduce side effects, resulting in the development of the modern sulfonamides. Many of the sulfonamides are no longer used as parenteral agents, but they continue to be used as topical agents or for treatment in specific conditions, such as prophylaxis for drug-resistant malaria. Some of these agents are no longer available in the U.S. but are still commonly used in other countries.

MECHANISM OF ACTION

The sulfonamides are bacteriostatic, exerting their effect as competitive antagonists of para-aminobenzoic acid (PABA). They inhibit dihydropteroate synthase from using PABA to synthesize dihydropteroic acid, a precursor of folic acid. The lack of folic acid intermediates ultimately results in impaired synthesis of nucleotides. Bacteria that use pre-formed folate are not susceptible to the bacteriostatic action. Silver sulfadiazine is one exception, as it exerts its effects on the cell membrane and cell wall and is bactericidal. The mechanism of action of mafenide is not known.

Unfortunately, bacterial resistance to sulfonamides is common, with cross-resistance between agents frequently occurring. Mutations that result in additional production of PABA or changes in the enzyme binding sites for sulfonamides are responsible for the resistance [116]. Genes for these resistant mutations may be carried on plasmids, allowing rapid transfer to other similar bacteria and resulting in more rapid development of resistance patterns than through random mutation alone [117].

One method for improving bacterial activity against potentially resistant strains is the addition of trimethoprim [118]. Trimethoprim is a competitive inhibitor of dihydrofolate reductase, another enzyme active in the synthesis of folate. Trimethoprim resistance is also common [119].

PHARMACOKINETICS

The sulfonamides can be divided into 4 groups based on absorption and excretion attributes. They are classified as short- to medium-acting agents, long-acting agents, agents limited to activity in the GI tract, and topical agents.

The Short- to Medium-Acting Sulfonamides

The first group, the short- to medium-acting agents, includes sulfisoxazole, sulfamethoxazole, and sulfadiazine. Sulfisoxazole is partly metabolized to N-acetyl sulfisoxazole; both the drug and the metabolite are excreted in the urine [120]. Because of a limited spectrum of action, sulfisoxazole is indicated primarily for uncomplicated urinary tract infection and chloroquine-resistant malaria. Sulfamethoxazole is combined with trimethoprim and is indicated for *Pneumocystis jiroveci* prophylaxis and treatment, upper respiratory tract infections, and urinary tract infections. The only FDA indication for sulfadiazine is toxoplasmosis [149].

The Long-Acting Sulfonamides

The long-acting agents have been associated with severe allergic reactions and for the most part been replaced in use by the less-toxic sulfonamides. The only long-acting agent still available is sulfadoxine, which is given as a combination with pyrimethamine. This drug is reserved for use for the treatment of drug-resistant malaria and may be used for treatment of *Toxoplasma gondii*. Pyrimethamine inhibits dihydrofolate reductase in *Plasmodium* species during the erythrocytic stage [149].

Sulfadoxine/pyrimethamine is absorbed quickly from the small intestine and, like the shorter acting agents, is widely distributed in tissue and body fluids [149].

THE SULFONAMIDES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Short- to Medium-Acting					
Sulfadiazine	1 every 12 hrs for 2 days	2 to 12 mos: 500 mg/day for 2 days 1 to 12 yrs: 500 mg every 12 hrs for 2 days	PO	Rash, pruritus	Multiple drug interactions. Contraindicated in infants <2 mos of age.
Sulfamethoxazole/trimethoprim	PO: 1 DS tablet every 12 to 24 hrs IV: 8-20 mg TMP/kg/day in 2-4 divided doses	PO: 8-12 mg TMP/kg/day in 2 divided doses	PO, IV	Rash, pruritus	Multiple drug interactions.
Sulfisoxazole	Initial: 2-4 g Maintenance: 4-8 g/day in 4-6 divided doses	Initial: 75 mg/kg Maintenance: 120-150 mg/kg in 4-6 divided doses Max: 6 g/day	PO	Rash, pruritus	Multiple drug interactions. Only in combination with erythromycin for pediatrics. Contraindicated in infants <2 mos of age.
Long-Acting					
Sulfadoxine/pyrimethamine	3 tablets	2 to 11 mos: ¼ tablet 1 to 3 yrs: ½ tablet 4 to 8 yrs: 1 tablet 9 to 14 yrs: 2 tablets >14 yrs: Use adult dosing	PO	Folic acid deficiency, blood dyscrasias, GI upset	For malaria prophylaxis: A single dose should be carried for self-treatment in the event of febrile illness when medical attention is not immediately available. Larger doses are recommended for treatment of active malaria.
Limited to GI Tract					
Sulfasalazine	Initial: 0.5-1 g every 6 to 8 hrs Maintenance: 2 g/day in divided doses	>2 yrs: 40-60 mg/kg/day in 3-6 divided doses	PO	Anorexia, headache, GI upset	Contraindicated with hypersensitivity to salicylates, sulfasalazine, sulfonamides, or mesalamine. Used for treatment of ulcerative colitis and rheumatoid arthritis.

Table 7 continues on next page.

THE SULFONAMIDES (Continued)					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Topical					
Mafenide acetate	Cream: Apply 1.6 mm layer to burn area every 12-24 hrs Solution: Wet dressing gauze every 4 hrs or as needed	Same as adults	5% topical solution, cream	Burning at application site, rash, allergic reaction	Used for treatment of second- and third-degree burns.
Silver sulfadiazine	Cream: apply 1.6 mm layer to burn area every 12 hrs	Not studied for pediatric use	Cream	Rash, allergic reaction	Used in the treatment of burns to prevent infection.
Sulfacetamide	Dosage varies with the preparation.	Not studied for pediatric use	Prepared in complex with other topical medications as a solution or ointment	Rash, local irritation	Combinations with fluometholone, prednisolone, and phenylephrine are available, each with differing dosing, indications, and contraindications. Common for ophthalmic use.
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. DS = double strength; TMP = trimethoprim.					
Source: [148; 149]					Table 7

Sulfonamides Limited to Gastrointestinal Tract Activity

The agents limited to the GI tract are very poorly absorbed and have been used for reducing bacterial flora in the bowel before surgery. The only available agent in this class is sulfasalazine, which is used in the treatment of ulcerative colitis. Although absorption of sulfasalazine from the intact intestine is very low, inflammation in the bowel may result in significant absorption of the metabolite sulfapyridine.

Topical Sulfonamides

The topical sulfonamides include mafenide acetate and silver sulfadiazine, which are used in the treatment of burns. Mafenide acetate is used less often because it may cause a metabolic acidosis as a result of carbonic anhydrase inhibition. An additional topical agent is sulfacetamide, which is used in ophthalmic and lotion formulations. Topical sulfonamides may be absorbed systemically, and if large burn areas are treated, absorption may be significant [149].

ABSORPTION/ELIMINATION

The sulfonamides are quickly absorbed after administration unless they have been altered to stay in the lumen of the intestine (e.g., sulfasalazine). After absorption, they are acetylated in the liver into a toxic but inactive form. The acetylated form is mostly excreted in the urine, with a small amount excreted in bile. These drugs are widely distributed throughout body tissue and fluids, including the CSF and peritoneal fluid [121].

The sulfonamides undergo acetylation and glucuronidation in the liver. Both the unchanged and metabolized forms are excreted in the urine through glomerular filtration and renal tubular secretion.

Mafenide may be used in renal failure, but monitoring of acid-base balance is recommended. Dosage and frequency of administration of other sulfonamides must be adjusted in renal failure based on serum levels. No data is available on dosing in hepatic insufficiency.

TOXICITIES/SIDE EFFECTS

Allergic reactions with rash and itching are relatively common. Nausea, vomiting, diarrhea, headache, and photosensitivity may occur. Rare but severe hypersensitivity reactions, including vasculitis, anaphylaxis, serum sickness, and Stevens-Johnson syndrome, may occur [122]. Sulfacetamide lotion also contains metabisulfite, which may cause an allergic reaction in patients allergic to sulfites.

Sulfonamide ophthalmic preparations may cause local irritation. The topical mafenide may cause pain or burning locally. Systemic reactions may develop during treatment with ophthalmic and topical preparations of sulfonamides due to systemic absorption.

Less common reactions include metabolic acidosis that may occur with absorption of mafenide due to a by-product, (rho) carboxybenzenesulfonamide, that inhibits carbonic anhydrase. Very rare reactions with sulfonamides include blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia, hemolytic anemia), hepatitis and hepatocellular necrosis, and toxic nephrosis due to crystaluria [123]. Hemolysis is more likely to develop in patients with G6PD deficiency [124].

Sulfonamides are contraindicated in patients who are known to be allergic to sulfa drugs and in cases where there have been previous adverse effects to sulfonamides.

DRUG INTERACTIONS

Warfarin, phenytoin, and sulfonamides may all be potentiated due to displacement of the drugs from serum albumin by the sulfonamides [125]. Cyclosporin levels may be decreased, and levels should be monitored [126]. Administration of PABA may antagonize the effects of sulfa drugs.

SPECIAL POPULATIONS

Sulfa drugs should be avoided in pregnancy near term due to the increased potential for kernicterus in the newborn [127]. Animal studies with sulfamethoxazole show bone abnormalities and a higher incidence of cleft palate.

Mafenide, sulfacetamide ophthalmic drops, and sulfadiazine are pregnancy category C. Sulfacetamide lotion has not been studied in pregnancy. Silver sulfadiazine is pregnancy category B, based on animal studies that showed no ill effects [128].

Sulfonamides are excreted in breastmilk. Sulfamethoxazole and sulfisoxazole are considered compatible with breastfeeding by the AAP, although they should be avoided if hyperbilirubinemia or G6PD deficiency is present [38]. Sulfacetamide lotion and silver sulfadiazine have not been studied in breastfeeding but would presumably also be excreted in breastmilk.

Because of the risk of neonatal kernicterus, use of sulfonamides should be avoided in the newborn. Pediatric use of sulfacetamide lotion has not been studied in children younger than 12 years of age, and sulfacetamide eye drops have not been studied in children younger than 2 months of age. Silver sulfadiazine has not been studied in pediatric patients [149].



The American Society for Gastrointestinal Endoscopy recommends that sulfonamides be avoided during the third trimester of pregnancy and when nursing infants younger than 2 months because of the risk of kernicterus.

(http://www.guideline.gov/summary/summary.aspx?doc_id=6822.

Last accessed January 14, 2009.)

Level of Evidence: B (observational studies) and C (expert opinion)

TETRACYCLINES

Chlortetracycline, the first tetracycline, was developed in 1948 as a product of *Streptomyces aureofaciens*. Chlortetracycline was altered to produce tetracycline. Doxycycline and minocycline are semisynthetic derivatives.

Tetracyclines bind to the 30S ribosomal subunit, blocking the binding of aminoacyl transfer-RNA [129]. This results in inhibition of protein synthesis, with bacteriostatic effects.

Bacterial resistance is typically the result of mutations that either prevent entrance of tetracyclines into the cell or increase the export of tetracycline out of the cell [130]. The resistance may be transmitted by plasmids [131].

PHARMACOKINETICS

The tetracyclines have a broad range of antibacterial effects, covering gram-positive, gram-negative, aerobic, and anaerobic bacteria. In addition, they also have activity against spirochetes and atypical bacteria, such as *Mycoplasma* and *Chlamydia* species [149].

The tetracyclines may be divided into three groups based on their pharmacokinetic traits. These groups are the short-acting group, intermediate-acting group, and long-acting group. The varying half-lives are the result of different rates of renal excretion [149].

Short-Acting Tetracyclines

The short-acting tetracyclines include oxytetracycline and tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. Oxytetracycline is no longer available in the United States [149]. Tetracycline has a broad spectrum of activity, with coverage of many aerobic gram-negative bacilli, atypical bacteria (such as *Chlamydia trachomatis*, *Chlamydia psittaci*, and *Mycoplasma pneumoniae*), and spirochetes, such as *Borrelia burgdorferi*. Tetracycline is also a second-line agent for *T. pallidum*. It is indicated by the FDA for treatment of rickettsial infections, typhus, Rocky Mountain spotted fever, trachoma, nongonococcal urethritis, and lymphogranuloma venereum. It is also commonly used for the treatment of acne [149].

Intermediate-Acting Tetracyclines

The only intermediate-acting agent available in the U.S. is demeclocycline. Demeclocycline is no longer used as an antibiotic but rather is used to treat the syndrome of inappropriate antidiuretic hormone (SIADH) [132].

Long-Acting Tetracyclines

The long-acting tetracycline agents, doxycycline and minocycline, are the more recently developed drugs. The main difference between these and the short-acting agents is that these may be dosed less frequently. The spectrum of bacterial coverage is essentially the same and the indications are the same, with the additional indication for the treatment of inhalation anthrax as part of a multidrug regimen.

THE TETRACYCLINES					
Agent	Adult Dosing Range	Pediatric Dosing Range*	Route	Common Side Effects	Comments
Short-Acting					
Tetracycline	250-500 mg every 6 hrs	25-50 mg/kg/day in 4 divided doses	PO	Photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption.
Intermediate-Acting					
Demeclocycline	150 mg every 6 hrs or 300 mg every 12 hrs	8-12 mg/kg/day in 2-4 divided doses	PO	GI upset, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Long-Acting					
Doxycycline	100-200 mg/day in 1-2 divided doses	2-5 mg/kg/day in 1-2 divided doses Max: 200 mg/day	PO IV	Photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Minocycline	Initial: 200 mg Maintenance: 100 mg every 12 hrs Max: 400 mg/day	Initial: 4 mg/kg Maintenance: 2 mg/kg every 12 hrs	PO	GI upset, tooth enamel deformities in children <8 yrs of age	
Prescribing information is given for comparison purposes only. The higher dosage ranges reflect dosages for more severe infections. Please consult the manufacturer's package insert for the antibiotic for complete prescribing information, maximum dosages, and indications. *All pediatric doses are for children older than 8 years of age.					
Source: [148; 149]					Table 8

ABSORPTION/ELIMINATION

Tetracycline is well absorbed after an oral dose taken in the fasting state. Doxycycline and minocycline are well absorbed after an oral dose and may be given with or without food.

The tetracyclines are well distributed throughout body tissues and fluids; distribution in the CSF is adequate for the treatment of some infections [133; 134]. The excellent tissue penetration results in the ability of the drug to cross into the dentin (bone and tooth enamel), where the tetracycline permanently chelates with the calcium [135].

Most of the tetracycline dose is excreted unchanged into the urine by glomerular filtration, although there is some biliary excretion as well. Doxycycline and minocycline are mostly excreted by nonrenal, possibly hepatic, routes. Only 20% to 26% of doxycycline and 4% to 19% of minocycline is excreted in the urine [136].

Tetracycline should be avoided in the presence of renal insufficiency, because it accumulates rapidly in the serum in the presence of decreased renal function. Doxycycline may be used in renal failure, as it will be excreted into the bile [137].

Because tetracyclines have been known to cause hepatic toxicity, they should not be used in patients with hepatic insufficiency [138].

TOXICITIES/SIDE EFFECTS

Tetracyclines commonly cause GI upset, including nausea, vomiting, and diarrhea. They also cause staining and deformity of the teeth in children younger than 8 years of age. Photosensitivity, pseudotumor cerebri, esophageal ulceration, and hepatotoxicity occur rarely [149].

Minocycline is often associated with vertigo, nausea, and vomiting, and it may increase azotemia in renal failure. In addition, prolonged use of minocycline may cause reversible discoloration of the fingernails, the sclera, and the skin [139]. Minocycline has been associated with a lupus-like reaction [140].

Allergic reactions to tetracyclines are not common but may range from mild rashes to anaphylaxis. Tetracyclines are contraindicated in patients who have shown hypersensitivity to any tetracyclines.

DRUG INTERACTIONS

Several types of drug interactions result in alterations in serum levels of tetracyclines. Agents that alkalize the urine will increase excretion of the tetracyclines. Polyvalent metal cations (calcium, aluminum, zinc, magnesium, and iron) and bismuth decrease absorption [141]. Drugs that induce hepatic enzymes may decrease the half-life of doxycycline.

Interactions that affect the efficacy of other drugs also occur. The bactericidal effect of penicillins may be decreased by co-administration with tetracyclines. Concurrent use of oral contraceptives may make the contraceptive less effective [142; 143]. The effects of warfarin are increased, probably because tetracyclines depress plasma prothrombin activity, resulting in a synergistic effect [144]. Digoxin effects may be increased because of changes in the bowel flora that are responsible for digoxin metabolism [145].

SPECIAL POPULATIONS

Tetracycline and doxycycline are pregnancy category D because of impaired bone development in the fetus. Hypoplasia of the enamel and discoloration of fetal teeth may occur, and maternal hepatic toxicity has been reported as well [146; 147].

Tetracyclines are excreted into the breastmilk in small amounts. Most exposed infants have very low blood levels of the drug and probably are not at risk [38]. Tetracyclines should not be used in children younger than 8 years of age because of the risk for tooth deformity.

CONCLUSION

Antibiotics are commonly used drugs that are diverse in their actions and side effects. The large number of antibiotics available makes it challenging to understand the characteristics of each of these antimicrobial agents, including important information such as toxicities and indications. Knowing the general characteristics of the classes of antibiotics makes it easier to recall the specific characteristics of agents within those classes, including newly introduced and future drugs.

Understanding the indications and antimicrobial effects of the antibiotic classes also makes it easier for the practitioner to tailor antibiotic treatment. This will lessen the likelihood of the development of microbial resistances, diminish side effects, and more effectively treat infections.

It is important to remember that the indications given by the FDA are guidelines. Many antibiotics are used for off-label purposes, and they may be used in doses that differ from the recommended doses, particularly for severe and life-threatening infections or for special populations, such as premature infants, neonates, and the elderly. Before using a specific agent, carefully review the detailed information offered in the package insert.

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