

# Antibiotics Review

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### Faculty

**Donna Coffman, MD**, attended medical school at the University of Louisville and completed her residency in Family Practice at St. John's Mercy Medical Center in St. Louis, Missouri. She is board-certified in Family Medicine and currently on staff at John Cochran VAMC in St. Louis.

### Faculty Disclosure

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

### Division Planner

Mark J. Szarejko, DDS, FAGD

### Senior Director of Development and Academic Affairs

Sarah Campbell

### Division Planner/Director Disclosure

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

### Audience

This course is designed for dental providers who prescribe and administer antibiotics to patients.

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### **Disclosure Statement**

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### **Course Objective**

The purpose of this course is to provide a review of the major classes of antibiotics and their characteristics as well as an overview of selected individual agents within each class that are most useful for today's clinical practitioner.

### **Learning Objectives**

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

1. Describe the general characteristics and mode of action of antibiotics commonly in use.
2. Employ best practice principles for limiting the emergence and transmission of antimicrobial-resistant strains within the healthcare environment, including in surgical practices.
3. Discuss the mechanism of action, pharmacokinetics, and spectrum of activity of natural and extended-spectrum penicillins.
4. Select the most appropriate, cost-effective cephalosporin based on "generational" characteristics and spectrum of activity.
5. Describe the role of carbapenems and monobactams.
6. Discuss the characteristics, expected toxicities, and indications for the use of aminoglycosides, macrolides, and sulfonamides.
7. Outline the mechanism of action, pharmacokinetics, and advantages inherent to quinolones and the 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 added regularly. This course is intended as an overview of the general characteristics of the major antibiotic classes, emphasizing mechanism of action, pharmacokinetics, and potential toxicities, with a brief discussion of the individual member agents and their clinical indications. The purpose of this course is to enlarge clinical perspective and enhance the understanding and confidence required for the selection of appropriate therapy of bacterial infections. The goal is to improve efficacy and safety while limiting the risk for selection and transmission of antimicrobial-resistant pathogens.

Given the large array of available antimicrobial agents, the scope of this course is confined to the eight major classes of antibiotics commonly employed for acute bacterial infection: the penicillins, cephalosporins, carbapenems, aminoglycosides, quinolones, macrolides, sulfonamides, and tetracyclines. A brief discussion of vancomycin, daptomycin, and newer glycopeptide analogues available for treatment of multi-resistant *Staphylococcus aureus* (MRSA) and enterococcal species is included.

For the purposes of the course, it is impractical to list or describe all the possible adverse effects, recommended uses, and off-label uses of the antibiotics discussed. Before using any antimicrobial, it is important to 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 such as anaphylaxis and the Stevens-Johnson syndrome. In some cases, there is a cross-sensitivity between agents in different classes. In addition, all antibiotics exert some impact on normal body flora as well as pathogens, in some cases leading to the emergence of *Candida* species and pathogenic bacteria such as *Clostridioides difficile*. Overgrowth of *C. difficile* within intestinal flora is often a serious complication of antimicrobial therapy that can produce symptoms ranging from mild diarrhea to severe, life-threatening pseudomembranous colitis [1]. Most cases resolve with supportive care and discontinuation of the offending antibiotic, but many require treatment. Furthermore, *C. difficile* colitis can develop days or weeks after the primary antimicrobial has been discontinued. A high degree of suspicion and judicious use of laboratory testing are the keys to recognizing and managing these complications.



According to the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America, the infusion of bezlotoxumab should be performed while a patient is receiving standard-of-care antibiotics and has been shown to be effective in preventing recurrent *C. difficile* infection if administered at any time before ending antibacterial treatment

(<https://academic.oup.com/cid/article/73/5/e1029/6298219>. Last accessed January 11, 2024.)

**Strength of Recommendation:** Expert Opinion/Consensus Statement

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## ANTIBIOTIC RESISTANCE

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Repeated exposure to an antibiotic may lead to the emergence of selective subpopulations of the same or related bacteria now resistant to the therapeutic agent. The Centers for Disease Control and Prevention (CDC) note that approximately 2.8 million people become infected with bacteria that are resistant to antibiotics, and approximately 35,000 people die annually because of these infections [2]. When *C. difficile* colitis, not typically resistant but associated with antimicrobial use, is added to these, the U.S. toll of all threats exceeds 3 million infections and 48,000 deaths [2]. Mechanisms of microbial resistance include altered cellular permeability (leading to greatly diminished intracellular concentration of the drug), increased efflux of the antibiotic from the cell, and elaboration of deactivating enzymes that alter the antibiotic's interaction at binding sites within the cell wall or cytoplasm [3].

Decreased cell membrane permeability is an important mechanism of bacterial resistance to beta-lactams, quinolones, and vancomycin. Microbial resistance to tetracyclines and quinolones is often mediated by increased efflux of the antibiotic from the cell. Enzymatic deactivation by beta-lactamases is the common mechanism of resistance to penicillins and cephalosporins. Resistance to aminoglycosides may result from altered cytoplasmic membrane transport (influx) or from intracellular enzymes (e.g., phosphotransferases and acetyltransferases) that deactivate the drug.

There are various mechanisms by which the interaction of an antibiotic with its binding site may be altered or bypassed, resulting in loss of antimicrobial activity. One such example, affecting the target site for quinolone activity, is an acquired structural alteration of deoxyribonucleic acid (DNA) gyrase, an enzyme essential for bacterial DNA synthesis. As a result, quinolones are no longer able to bind to the enzyme and the drug loses its antimicrobial effect.

Another example is the methylation of ribosomal ribonucleic acid (rRNA) that prevents the binding of macrolides. The effectiveness of trimethoprim/sulfamethoxazole, which acts through disruption of folate synthesis by the cell, may become diminished by the adaptive ability of some bacteria to utilize an alternate metabolic pathway, thereby avoiding the effects of trimethoprim [4].

These resistance mechanisms 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 succumb to the action of the antibiotic, the subpopulation that has the adaptive mutation continues to replicate, replacing the original population with a resistant one.

Bacterial resistance can be transferred from one bacterium to another, or from one bacterial species to related group, by means of plasmids or transposons that gain entry to the cell. 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 many nearby bacteria, which may or may not be the same species. In this manner, resistance can quickly spread from species to species [5].

Many strategies have been used to circumvent the multiple mechanisms of resistance encountered in bacteria. Among these are addition of beta-lactamase inhibitors to extended-spectrum penicillins, alteration of cephalosporin side chains to produce new generations of the drug with broader activity, and combining drugs to enhance the antimicrobial effect (e.g., sulfamethoxazole with trimethoprim). In 2021, in response to perceived overuse of antibiotics, the American College of Physicians recommended limiting antibiotic courses to five to seven days for some of the most common bacterial infections, including durations of antibiotic therapy in patients with common bacterial infections, such as acute bronchitis, community-acquired pneumonia, urinary tract infection, and cellulitis [172].



A meta-analysis published by the *Cochrane Database of Systematic Reviews* found high-certainty evidence that any professional or structural interventions are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment in the hospital setting.

([https://www.cochrane.org/CD003543/EPOC\\_improving-how-physicians-working-hospital-settings-prescribe-antibiotics](https://www.cochrane.org/CD003543/EPOC_improving-how-physicians-working-hospital-settings-prescribe-antibiotics). Last accessed January 11, 2024.)

**Level of Evidence:** Meta-analysis

In addition, new categories of antibiotics are being created to stay ahead of the rapid evolution of bacterial resistance. Linezolid and tedizolid, the only two FDA-approved drugs in the oxazolidinone category, are examples of this, with linezolid being the first of the two to be developed. Oxazolidinones are a unique category of drugs that prevent formation of the 70S protein synthesis complex in bacteria and may be useful in the treatment of vancomycin-resistant enterococci and MRSA [6; 7]. Nonetheless, development of resistance in bacteria is relentless.

Considering the efficient means by which bacteria develop resistance, clinicians should avoid, where possible, practice patterns that contribute to the process. In 2002, the CDC issued a position paper outlining recommendations for minimizing nosocomial infection and the emergence of resistant organisms [8]. In this paper, the CDC recommended a multistep approach that included: preventing infection (by paying careful attention to the proper use of invasive medical devices); tailoring medical treatment to fit the infection (by avoiding broad-spectrum antibiotics and prolonged treatment when possible); and preventing the transmission of resistant bacteria between patients (by emphasizing hand washing and implementing hospital infection control programs) [8]. Since issuance of the CDC's position paper, the agency has taken many additional steps and implemented coordinated, strategic action plans to change the course of antibiotic resistance. This includes publication of *The National Action Plan for Combating Antibiotic-Resistant Bacteria*

(CARB), 2020–2025 [9]. The CARB builds on the first National Action Plan, released in 2015, and prioritizes infection prevention and control to slow the spread of resistant infections and reduce the need for antibiotic use. The CARB also integrates a “one health” approach, which recognizes the relationships between the health of humans, animals, plants, and the environment [9]. It has also been hypothesized that the response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and associated COVID-19 illness might increase use of antibiotics and other antimicrobial medicines (both appropriate and inappropriate) to address primary or secondary infections, with the potential to further accelerate the emergence of antibiotic resistance despite the rate of the development of new antibiotics [9].

In 2022, the CARB Task Force issued a Year 5 Progress Report on combating antimicrobial-resistant bacteria, summarizing accomplishments achieved between 2015 and 2020. This report showed that substantial progress had been achieved for the following targeted bacteria: health care-associated *C. difficile* infection decreased by 36%; hospital-onset multidrug-resistant *Pseudomonas aeruginosa* decreased by 41%; and hospital-onset MRSA bloodstream infections decreased approximately 31.5% [173].

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## CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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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 [10].

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## PENICILLINS

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Alexander Fleming discovered penicillin 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 [11].

### MECHANISM OF ACTION

Penicillin is bactericidal, killing susceptible bacteria by interrupting cell wall synthesis. The drug exerts its effect by preventing cross-binding of the peptidoglycan polymers necessary for cell wall formation and by binding with carboxypeptidases, endopeptidases, and transpeptidase (“penicillin-binding proteins” [PBPs]) that participate in cell wall synthesis [12]. Although the exact mechanisms involved are not known, the 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 favorably modified.

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 [13]. In addition, some bacteria are able to prevent binding to the PBPs by various means, including altered binding sites for the penicillins [14].

Various strategies have been employed to circumvent these microbial adaptations. Altering the structure of the penicillin molecule 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 block bacterial beta-lactamases [6]. 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 spectrum of antibacterial activity. These groups are the natural penicillins, the aminopenicillins, the penicillinase-resistant penicillins, and the antipseudomonal penicillins [15].

#### The Natural Penicillins

The natural penicillins include various penicillin G preparations and penicillin V potassium. Penicillin G is very unstable in stomach acid and must be given parenterally. Penicillin V potassium is more acid-stable and is the appropriate form for oral administration.

The natural penicillins are active against gram-positive organisms such as streptococci, *Enterococcus faecalis*, and *Listeria monocytogenes*. However, most *S. aureus* isolates are now resistant. The natural penicillins are also active against anaerobic species, such as *Bacteroides* species and *Fusobacterium* species. At serum levels achieved by parenteral administration, the natural penicillins are effective against some gram-negative bacteria, such as *Escherichia coli*, *H. influenzae*, *Neisseria gonorrhoeae*, and *Treponema pallidum*. For the treatment of moderate-to-severe infections in which resistant organisms are considered a possibility, reliance upon penicillin alone should be avoided unless the identity and sensitivity of the infecting organism have been confirmed. Labeled uses include treatments for infections of the upper and lower respiratory tract, throat, skin, and genitourinary tract and prophylaxis of recurrent rheumatic fever and pneumococcal infections [6].

THE PENICILLINS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
<b>Natural Penicillins</b>					
Penicillin G benzathine	1.2-2.4 MU	50,000 U/kg in one dose Max: 2.4 MU divided between 2 injection sites	IM	Rash, GI upset	Indicated for syphilis and group A strep infections. Note: Do not administer IV (except parenteral/aqueous preparation) or IM near nerve or artery. Cardiopulmonary arrest and death have occurred from accidental IV administration.
Penicillin G benzathine or penicillin G procaine	2.4 MU in one dose	<14 kg: 0.6 MU 14 to 27 kg: 1.2 MU in one dose	IM	Rash, GI upset	
Penicillin G (parenteral/aqueous)	2-30 MU per day	100,000-400,000 U/kg/day in divided doses every 4 to 6 hours Max: 24 MU/day	IM, IV	Rash, GI upset	
Penicillin V potassium	125-500 mg every 6 to 8 hours	Pneumonia (off label): 50-75 mg/kg/day in 3 to 4 divided doses Pharyngitis: 250 mg 2 to 3 times per day	PO	Rash, GI upset	--
<b>Aminopenicillins</b>					
Amoxicillin	250-500 mg every 8 hrs, or 500-875 mg twice daily	Manufacturer recommendation: >3 months and <40 kg: 20-100 mg/kg/day in divided doses every 8 to 12 hrs ≤3 months: 20-30 mg/kg/day divided every 12 hrs  AAP recommendation: All infants and children <40 kg: 25-50 mg/kg/day in divided doses every 8 hrs	PO	Rash, diarrhea	Not to be confused with amoxicillin/clavulanate ES formulation. Extended-release tablet 775 mg once daily for adults and children ≥12 years of age
Amoxicillin/clavulanate	250-500 mg every 8 hrs, or 875 mg every 12 hrs	15-40 mg/kg/day divided every 8 hrs, or 25-45 mg/kg/day divided every 12 hrs Max: 4g/day <3 mos: 30 mg/kg/day every 12 hrs (125 mg/5 mL suspension only)	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 and requires product specific dosing.
Ampicillin	250-500 mg every 6 hrs	PO: 50-100 mg/kg/day in 4 divided doses Max: 2-4 g/day IV, IM: 25-200 mg/kg/day every 3 to 4 hrs Max: 12 g/day	PO, IV, IM	Rash, GI symptoms (very common)	The IV form can be given in divided doses or in a continuous infusion.

Table 1 continues on next page.

THE PENICILLINS (Continued)					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Ampicillin/sulbactam	1.5–3 g every 6 hrs IV	≥1 year: IV: 100–400 mg/kg/day every 6 hrs Max: 8 g/day	IV, IM	Rash, diarrhea, local pain at injection or infusion site (very common with IM use)	Dosing for ampicillin/sulbactam is based on the ampicillin component.
<b>Penicillinase-Resistant Penicillins</b>					
Dicloxacillin	125–500 mg every 6 hrs	<40 kg: 12.5–100 mg/kg/day in 4 doses divided every 6 hrs >40 kg: 125–250 mg every 6 hrs	PO	Rash, diarrhea	Use with caution in neonates, as elimination of drug is slow.
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: 50–200 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	0.25–2 g every 4 to 6 hrs	<40 kg: 50–100 mg/kg/day in divided doses every 6 hrs >40 kg: 250–1,000 mg every 4 to 6 hrs	IV, IM	Phlebitis at IV site, hepatitis, rash	Drug-induced hepatitis is usually reversible if drug is discontinued. Neonatal dosing may require the use of alternate container system/dosage forms. May contain a significant amount of sodium.
<b>Antipseudomonal Penicillins</b>					
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	–
Piperacillin/tazobactam	IV: 3.375–4.5 every 6 to 8 hrs Max: 18 g/day	Infants 2 to 9 months: 80 mg piperacillin/kg/dose every 8 hrs Infants and children >9 months: 100 mg piperacillin/kg/dose	IV	Rash, GI upset	Dosing for adults and pediatrics based on traditional infusion method (IV infusion over 30 minutes). Dosage in pediatric patients based on piperacillin component. Pediatric dose is mg/kg/dose, not mg/kg/day.
Ticarcillin or ticarcillin/clavulanate potassium	<60 kg: 200–300 mg/kg/day divided every 4 to 6 hrs >60 kg: 3.1 g every 4 to 6 hrs Max: 18 g/day	Use adult dosing by weight	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. AAP = American Academy of Pediatrics; MU = million units; ES = extra strength.					
Source: [6; 16]					

Table 1



## The Aminopenicillins

The aminopenicillins have about the same activity as the natural penicillins against susceptible gram-positive organisms, plus improved coverage of selected gram-negative bacilli, including *Enterobacteriaceae*. 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. These agents are useful for the management of sinusitis/bronchitis, endocarditis, meningitis, susceptible urinary tract infection, and salmonellosis [6]. Amoxicillin is the best absorbed of the oral penicillins. It is acid-stable and its absorption, unlike ampicillin, is not much affected by food. Improved absorption is also thought to provide an advantage over ampicillin in reducing the risk of antibiotic-associated diarrhea. Labeled uses include endocarditis prophylaxis and as a component of a multidrug *H. pylori* eradication regimen [6].

## The Penicillinase-Resistant Penicillins

The penicillinase-resistant penicillins were developed in response to the emergence of penicillinase-producing *S. aureus*. 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 United States [6].

Although penicillinase-resistant penicillins have the same spectrum of activity against many of the same gram-positive pathogens as the natural penicillins, they lack significant activity against gram-negative or anaerobic organisms. They are, however, notable for their usefulness against penicillin-resistant (methicillin-sensitive) *Staphylococcus* species.

## The Antipseudomonal Penicillins

The antipseudomonal penicillins are often also referred to as extended-spectrum penicillins; these include ticarcillin and piperacillin (both of which are parenteral). Mezlocillin, which was also parenteral, and carbenicillin, which could be administered orally, are no longer available in the United States [6; 17].

The extended-spectrum penicillins retain their activity against gram-positive bacteria and anaerobic gram-negative pathogens such as *Bacteroides fragilis*. However, these agents were developed because of their excellent activity against *Pseudomonas aeruginosa* and other multidrug-resistant gram-negative pathogens, including *Klebsiella* species and *Serratia* species. The antipseudomonal penicillins are effective for treatment of *H. influenzae* as well.

## The Addition of Beta-Lactamase Inhibitors

The addition of clavulanic acid, sulbactam, or tazobactam increases the spectrum of activity of the penicillin derivative with which they are combined. 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 [18].

## ABSORPTION/ELIMINATION

While most penicillins can be absorbed via the oral route, the bioavailability varies considerably, and food may interfere with absorption. Penicillin V, amoxicillin, ampicillin, and dicloxacillin can be given orally; the remaining penicillins are either too unstable in the acidic environment of the stomach or must be given intravenously in order to achieve sustained therapeutic levels. Amoxicillin is the best absorbed of the oral penicillins and the least affected by a recent meal.

Following oral administration and GI absorption, 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 (500 mg 4 times daily) [6; 19]. Concentration in urine is high due to renal clearance mechanisms.

Penicillins are excreted in the kidney by means 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 the penicillins are excreted to some degree in the bile, but biliary excretion is most important for antipseudomonal penicillins and nafcillin [20].

In patients with mild renal insufficiency, dosage adjustment is not needed, except with the use of ticarcillin [21]. If the creatinine clearance is less than 50 mL/min, then dosage adjustments of parenteral penicillins 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.

## **SIDE EFFECTS/TOXICITY**

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. However, studies have found that penicillin allergy is less common than previously thought [22; 23; 24; 25]. Traditionally, allergic reactions were believed to occur in up to 10% of patients; however, more recent studies have found the rate to be much lower. While penicillin-induced anaphylaxis death rate estimates are similar to previous statistics (i.e., approximately 0.002% among the general population), the percent-

age of individuals with a true penicillin allergy as defined by immunoglobulin E (IgE)-mediated reaction is generally less than 10%, with some studies showing a true penicillin allergy rate of only 0.7% [22; 23; 24; 26]. It is also important to note that approximately 90% of patients previously diagnosed with a penicillin allergy will show no reactivity if not exposed to the antibiotic for 10 years or more, due to the absence of a true allergy or loss of allergy over time [22; 24; 25]. Allergy skin testing is the most reliable way to determine true penicillin allergy and may allow for previously avoided antibiotics to be used as indicated.

Reactions commonly misdiagnosed as true 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 [6; 20]. These responses were originally thought to develop in response to the beta-lactam ring and its derivatives and, therefore, there is a common misperception that penicillins are cross-reactive with other antibiotics with the same beta-lactam structure (e.g., cephalosporins) [6]. However, the major determinant in the immunologic reaction is now recognized to be the similarity in the side chain of first-generation cephalosporins and penicillins (not the beta-lactam structure), with the reaction nearing 0% in third-generation cephalosporins [22; 23; 24].

Rarely, penicillins may cause hematologic reactions with neutropenia due to reversible bone marrow suppression. Abnormal platelet aggregation may occur, particularly with ticarcillin [27]. 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 activity of penicillin is diminished. The antipseudomonal penicillins also may affect warfarin metabolism. Therefore, the prothrombin time, using the international normalized ratio (INR), should be monitored [6; 28].

## SPECIAL POPULATIONS

The penicillins are pregnancy category B, indicating no adverse events noted in animal studies [6; 29]. These agents are secreted in breast milk, and breastfeeding should be avoided if the infant is allergic to any of the penicillins [30]. Use while breastfeeding may cause modifications of normal intestinal flora and allergic sensitization in the infant [6].

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## CEPHALOSPORINS

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Giuseppe Brotzu discovered the first cephalosporin in 1948, observing 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 [31].

### 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 as that for 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 [32; 33].

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 cephalosporins results 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 [34].

An additional source of resistance in gram-negative bacteria is alteration in the cell-membrane porins that normally allow passage of the cephalosporins into the cell [35].

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 [36].

### PHARMACOKINETICS

The cephalosporins have been classified in different ways, based on chemical structure and pharmacologic activities. The conventional classification for clinical purposes groups cephalosporins into “generations” based on when they were developed and similarities in antimicrobial coverage.

#### First-Generation Cephalosporins

The first-generation cephalosporins are most active against aerobic gram-positive cocci. These agents include cefazolin, cephalexin, and cefadroxil, and they are often used for skin infections caused by *S. aureus* and *Streptococcus* and for susceptible urinary tract infections. 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*.

THE CEPHALOSPORINS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
<b>1st Generation</b>					
Cefadroxil	1-2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	PO	Rash, diarrhea	Can interfere with some urine glucose tests.
Cefazolin	1-2 g every 8 hrs Max: 12 g/day	>1 mo: 25-100 mg/kg/day divided every 6 to 8 hrs Max: 6 g/day	IV, IM	Phlebitis at infusion site, seizure, rash, diarrhea	Can interfere with some urine glucose tests.
Cephalexin	250-1,000 mg every 6 to 12 hrs Max: 4 g/day	>1 yr to <15 yrs: 25-100 mg/kg/day in 3 to 4 divided doses Max: 4 g/day	PO	GI upset, rash	Can interfere with some urine glucose tests.
<b>2nd Generation</b>					
Cefaclor	250-500 mg every 8 hrs	>1 mo: 20-40 mg/kg/day in 2 to 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 Max: 4-6 g/day	AAP recommendation: 30-50 mg/kg/dose every 12 hrs Max: 4,000 mg/day	IV, IM	Phlebitis at infusion site, rash, GI upset	Disulfiram-like reaction with alcohol. Can interfere with some urine glucose tests. Not recommended for treatment of community-acquired intra-abdominal infections.
Cefoxitin	1-2 g every 6 to 8 hrs Max: 12 g/day	>3 mos: 80-160 mg/kg/day in 4 to 6 divided doses Max: 12 g/day	IV, IM	Phlebitis at infusion site, rash	IM injection is painful. Can interfere with some urine glucose tests. In pediatrics, for group A beta-hemolytic streptococcal infections, antimicrobial therapy should be given for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis.
Cefprozil	250-500 mg every 12 to 24 hrs	>6 mos: 7.5-20 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 for 10 days IV, IM: 0.5-1.5 g every 6 to 8 hrs 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	Tablets and oral suspension forms require different dose. Oral doses noted here are for tablet formulation. Higher doses can be used for severe infection.
<b>3rd Generation</b>					
Cefdinir	300 mg every 12 hrs, or 600 mg every 24 hrs for 10 days	7 mg/kg/dose twice daily or 14 mg/kg/dose for 10 days Max: 600 mg/day	PO	Rash, diarrhea	Iron and antacids can reduce absorption. Can interfere with some urine glucose tests.
Cefditoren	200-400 mg every 12 hrs for 10 to 14 days	Not studied for patients <12 yrs	PO	GI upset, headache	Interaction with proton-pump inhibitors, H2 blockers, antacids. Contraindicated with milk protein allergy.

Table 2 continues on next page.

THE CEPHALOSPORINS (Continued)					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
<b>3rd Generation (Continued)</b>					
Cefixime	400 mg/day in 1 or 2 doses	>6 mos and <45 kg: 8–20 mg/kg/day every 12 to 24 hrs Max: 400 mg/day >12 yrs or >50 kg: Use adult dosing	PO	Diarrhea, rash	Can interfere with some urine glucose tests.
Cefotaxime	1–2 g every 4 to 12 hrs	1 mo to 12 yrs and <50 kg: 50–225 mg/kg/day in 3 to 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 for 7 to 14 days	10 mg/kg/day in 2 divided doses	PO	Diarrhea, nausea, vomiting	Decreased absorption with antacids and H2 blockers. Can be given as a single dose for GC.
Ceftazidime	500–1,000 mg every 8 hrs	IV: 30–50 mg/kg every 8 hrs Max: 6 g/day AAP recommendation for IV: 90–200 mg/kg/day every 8 hours 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 for 10 days	9 mg/kg/day Max: 400 mg/day for 10 days	PO	Rash, GI upset, headache	Can interfere with some urine glucose tests.
Ceftriaxone	IV, IM: 1–2 g every 12 to 24 hrs	50–100 mg/kg/day in 1 to 2 divided doses Max: 4 g/day	IV, IM	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 detectable abnormalities.
<b>4th Generation</b>					
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.
Cefiderocol	2 g every 8 hours for 7 to 10 days	–	IV	Phlebitis at infusion site, rash, GI upset	Can interfere with some urine glucose tests
<b>5th Generation</b>					
Ceftaroline fosamil	600 mg every 12 hours for 5 to 14 days	>2 mos to <2 yrs: 8 mg/kg dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and <33 kg: 12 mg/kg/dose every 8 hrs for 5 to 14 days >2 yrs to <18 yrs and >33 kg: 400–600 mg every 8 to 12 hrs for 5 to 14 days	IV	Phlebitis at infusion site, GI upset, headache	Slow IV infusion over 60 minutes. Can interfere with some urine glucose tests.
Ceftobiprole	500 mg every 8 hours	–	IV	Hyponatremia, phlebitis at infusion site, headache, nausea/vomiting	Approved for use in Canada but not the United States. Not for use in patients with ventilator-associated pneumonia.
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. GC = gonococcal infection.					
Source: [6; 16]					

Table 2

### Third-Generation Cephalosporins

The third-generation cephalosporins have enhanced activity and a broader spectrum against gram-negative organisms, including *Neisseria* species, *M. catarrhalis*, *Klebsiella*, and other *Enterobacteriaceae*. Of these agents, ceftriaxone has the best activity against gram-positive cocci, specifically *S. pneumoniae* and methicillin-sensitive *S. aureus*. Ceftazidime is active against *P. aeruginosa*. Other cephalosporins in this class include cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftibuten, and ceftriaxone. These drugs are useful for more severe community-acquired respiratory, intraabdominal, and urinary tract infections and for nosocomial infections (because of the high incidence of resistant organisms) [37].

### 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.

### Fifth-Generation Cephalosporins

Ceftaroline fosamil is a novel advanced-generation cephalosporin approved by the U.S. Food and Drug Administration (FDA) in 2010, for the treatment of community-acquired bacterial pneumonia and bacterial skin and soft-tissue infections [6]. As with other beta-lactams, ceftaroline exerts its antimicrobial effect by binding to PCP and inhibiting cell wall synthesis. This agent is unique in that it also has a high affinity for PBP2a, which is associated with resistance to methicillin. Consequently, ceftaroline is highly active against methicillin-sensitive and resistant strains of *S. aureus* and against multidrug-resistant *S. pneumoniae* [38]. It is ineffective for *P. aeruginosa*, and its activity against *Enterobacteriaceae* is variable. Beta-lactamase-producing *Enterobacteriaceae*

and AmpC mutants are resistant. Prospective clinical trials have shown that the efficacy of ceftaroline is comparable to vancomycin plus aztreonam for the treatment of bacterial skin and soft-tissue infection (including methicillin-resistant *S. aureus* [MRSA]) and to ceftriaxone for the treatment of community-acquired bacterial pneumonia [39]. Among cases of pneumonia caused by *S. pneumoniae*, clinical cure rates were higher with ceftaroline (83.3%) than with ceftriaxone (70%) in a phase III clinical trial, and the agent was well tolerated [40].

Ceftobiprole is a fifth-generation cephalosporin with a broad spectrum of antimicrobial activity, including drug-resistant pneumococci, *P. aeruginosa*, and methicillin-resistant *S. aureus* (MRSA). The drug is approved for the treatment of community- and hospital-acquired pneumonia in Canada and parts of Europe. The results of a pivotal clinical trial of patients hospitalized with community-acquired pneumonia treated with ceftobiprole showed a high rate of clinical cure [41; 42; 43].

### ABSORPTION/ELIMINATION

The orally administered cephalosporins include cefaclor, cefadroxil, cephalixin, cefprozil, cefuroxime axetil, cefixime, cefpodoxime proxetil, ceftibuten, and cefdinir. In general, the orally administered cephalosporins are absorbed rapidly. Cephalixin, 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 [44].

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, and cephalexin 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 H<sub>2</sub> antagonists [45].

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 ceftaroline all have good penetration into the CSF [38; 46].

Most cephalosporins are eliminated by the kidney. The exception in the oral cephalosporins is cefixime, half of which is excreted in the urine [6]. The remaining half is metabolized in the liver to inactive metabolites and partly excreted in the bile. Cefotaxime is deacetylated by the liver to a bioactive metabolite and inactive forms. The deacetylated metabolites are excreted by the kidney. Cefditoren is excreted predominantly in the bile.

In severe hepatic insufficiency, compensatory changes in renal excretion of the hepatically metabolized drugs may occur [47]. In the presence of severe renal and/or hepatic insufficiency, dosage adjustment of cefotaxime is necessary.

### **SIDE EFFECTS/TOXICITY**

As a group, cephalosporins are relatively well tolerated [48]. 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. Infrequently, there is some cross-sensitivity with true penicillin allergy (estimated nearly 0% to 10%

of cases); this occurs mostly with first-generation cephalosporins [21; 22; 23; 24]. If a patient develops urticaria, anaphylaxis, or angioedema with penicillins or a cephalosporin, avoid using any of the other cephalosporins.

Although uncommon, nephrotoxicity has been reported [49]. 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 and cholestatic hepatitis due to precipitation in bile [50; 51]. Rare reactions include hematologic toxicity with resultant eosinophilia, thrombocytopenia, and leukopenia, all of which resolve after stopping treatment [52]. Rarely, hemolytic anemia develops [53]. 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 [54]. 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 many cephalosporins [6; 55].

### **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 [6].

### **SPECIAL POPULATIONS**

Cephalosporins are generally considered safe to use in pregnancy and are designated as category B. They are excreted in breast milk in low concentrations, and the American Academy of Pediatrics (AAP) considers this compatible with breastfeeding [6; 56; 57].

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## CARBAPENEMS

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Meropenem, imipenem/cilastatin, doripenem, and ertapenem are parenteral synthetic beta-lactams derived from thienamycin, an antibiotic produced by *Streptomyces cattleya* [58]. They have a lactam ring, like the penicillins and cephalosporins, but have a methylene moiety in the ring. The newest carbapenem is combination imipenem/cilastatin/relebactam [6].

### 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 not allowing transport of the drug into the cell [59]. Cross-resistance may occur between the carbapenems.

### PHARMACOKINETICS

Imipenem and ertapenem have a wide antimicrobial spectrum with excellent activity against enteric gram-negative bacilli and pseudomonas as well as anaerobic bacteria, including *Bacteroides* species. They also cover many gram-positive cocci, such as *Enterococcus* and *Streptococcus* [60]. 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 approved by the FDA for use in urinary tract infections, pneumonia, intra-abdominal infections, and skin and soft-tissue infections [6]. 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 [6]. Combination meropenem/vaborbactam is approved for the

treatment of complicated urinary tract infections caused by susceptible micro-organisms [6; 61]. The combination imipenem/cilastatin/relebactam was approved by the FDA in 2019 for the treatment of complicated urinary tract infections and complicated intra-abdominal infections [6; 62].

### ABSORPTION/ELIMINATION

Imipenem/cilastatin, imipenem/cilastatin/relebactam, 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 hydrolysing 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 [63]. The addition of relebactam to imipenem protects imipenem from degradation by certain serine beta-lactamases [6]. Meropenem, doripenem, and ertapenem do not require a dehydropeptidase I inhibitor.

Following administration, meropenem penetrates well into body tissues and fluids, including the CSF. Imipenem/cilastatin/relebactam and ertapenem are distributed throughout body tissues, but with only low concentrations in the CSF [64].

Most of the imipenem/cilastatin and imipenem/cilastatin/relebactam doses are excreted in the urine [6]. 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 secretion [65]. 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.



## SIDE EFFECTS/TOXICITY

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 [66]. Hypersensitivity reactions may occur, and while there is a degree of cross-sensitivity with penicillins, this risk is lower than previously believed [22; 23; 24]. Carbapenems should be used with caution in patients allergic to the carbapenems or penicillins [6].

## DRUG INTERACTIONS

There are few drug interactions associated with the carbapenems, but probenecid may increase the serum levels of meropenem, ertapenem, imipenem/cilastatin, and imipenem/cilastatin/relebactam and should be avoided. Ertapenem cannot be infused with dextrose or other medications. Meropenem may reduce levels of valproic acid [67].

## SPECIAL POPULATIONS

Meropenem, doripenem, and ertapenem are pregnancy category B, with animal studies showing no adverse reactions [68]. Imipenem/cilastatin is pregnancy category C, based on studies in monkeys that showed increased embryonic loss and side effects in the mother [69]. No pregnancy category has been assigned to imipenem/cilastatin/relebactam [6; 70]. No data are available regarding breastfeeding and carbapenem administration.

The safety of doripenem 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 [6; 71]. Ertapenem can be used in infants older than 3 months of age, and imipenem can be used from birth; these agents are useful for treating complicated infections in pediatric patients (e.g., complicated urinary tract infections).

## MONOBACTAMS

Monobactams have a single beta-lactam core, distinguishing them from the other beta-lactam drugs [72]. 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 as an alternative therapy for gram-negative bacterial infections, including *P. aeruginosa* and *Klebsiella*, that are resistant to the first-line beta-lactams or carbapenems. 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.

There is no oral form of aztreonam, and intravenous is the preferred mode of parenteral administration. It is distributed widely in body tissues and fluids, including inflamed meningeal tissue [6; 73]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [6; 74]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [6; 75].

THE OTHER BETA-LACTAMS					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
<b>Carbapenems</b>					
Doripenem	500 mg every 8 hours for 5 to 14 days	Not studied for pediatric use	IV	Headache, rash, nausea, vomiting, diarrhea, phlebitis	Dosage adjustment necessary for renal impairment. Cannot be used in patients with known serious hypersensitivity or history of anaphylaxis to any beta-lactam antibiotic. Seizure risk in patients with CNS disorders.
Ertapenem	1 g/day for 3 to 14 days	15 mg/kg every 12 hrs Max: 1 g/day for 3 to 14 days	IV, IM	Diarrhea, nausea, phlebitis at infusion site	Seizure risk in patients with CNS disorders. IV therapy may be administered for up to 14 days; IM for up to 7 days.
Imipenem/cilastatin	500–1,000 mg every 6 to 8 hrs Max: 4 g/day	>3 mos: 15–25 mg/kg every 6 hrs Max: 4 g/day	IV	Phlebitis at infusion site, rash	Documentation of cross-allergy with penicillin allergy is limited. Seizure risk in patients with CNS disorders. Adults <70 kg may require decreased dosing.
Imipenem/cilastatin/relebactam	1.25 g every 6 hours for a 5-14 days	N/A	IV	Anemia	Documentation of cross-allergy with penicillin allergy is limited. Seizure risk in patients with CNS disorders.
Meropenem	1.5–6 g/day in 3 divided doses	Infants <3 mos (IV): Gestational age <32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 12 hrs Postnatal age ≥14 days: 20 mg/kg/dose every 8 hrs Gestational age ≥32 weeks AND postnatal age <14 days: 20 mg/kg/dose every 8 hrs Postnatal age ≥14 days: 30 mg/kg/dose every 8 hrs >3 mos and <50 kg: 30–120 mg/kg/day in 3 divided doses Max: 6 g/day >50 kg: Same as adult dosing	IV	Diarrhea, nausea, inflammation at the injection site, headache	Can cause elevated LFTs. Seizure risk in patients with CNS disorders.
Meropenem/vaborbactam	4 g every 8 hrs for <14 days	Not studied in pediatric patients	IV	Headache, GI symptoms, phlebitis at infusion site	Dosage adjustment necessary for renal impairment.

Table 3 continues on next page.

## THE OTHER BETA-LACTAMS (Continued)

Monobactams					
Aztreonam	IV: 1–2 g every 8 to 12 hrs  Nebulizer: 75 mg 3 times/day at least 4 hours apart for 28 days; do not repeat for 28 days after completion.	>9 mos: 30–50 mg/kg/dose every 6 to 8 hrs Max: 120 mg/kg/day >7 years of age (nebulizer): Same as adult dosing	IV, IM, oral inhalation	Rash, nausea, vomiting, phlebitis at infusion site	Rare cross-sensitivity with allergy to other beta-lactams. For oral inhalation, pretreatment with a bronchodilator is recommended.
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: [6; 16]					Table 3

**SIDE EFFECTS/TOXICITY**

Frequent adverse reactions include elevations of liver enzymes and transient eosinophilia. Less common reactions include phlebitis at the infusion site, rash, diarrhea, and nausea [6; 76].

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 [77]. 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 [6; 78].

**SPECIAL POPULATIONS**

Aztreonam is pregnancy category B, based on animal studies that have shown no ill effects of the drug. There are no human data available [6].

Aztreonam is secreted in breast milk in low concentrations; breastfeeding is not recommended because the effects of the drug have not been studied in young infants [78].

Aztreonam has not been studied for use in children younger than 1 month of age but appears safe in children older than 1 month of age, although it should be noted that manufacturer recommendations are for children older than 9 months of age [6; 78]. It has been shown to be very useful in children with respiratory symptoms of cystic fibrosis [79].

**AMINOGLYCOSIDES**

The first aminoglycoside, streptomycin, was derived from *Streptomyces griseus* during the 1940s. Actinomycetes were studied for possible antimicrobial byproducts, and it was found that *Micromonospora* and *Streptomyces* produced useful agents. As newer, safer, and more effective aminoglycosides have been developed, the use of streptomycin is now confined primarily to certain management strategies for the treatment of tuberculosis.

**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 [80].

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 involves 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 [81].

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 [81].

To combat resistances and overcome the relative natural resistance of enterococcus, 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 makes the cell wall more permeable to the aminoglycosides [82].

## 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 beta-

lactam, vancomycin, or other agents active 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.

The aminoglycosides commonly used at present for treatment of systemic bacterial infection include gentamicin, tobramycin, and amikacin. Kanamycin is discontinued [17]. Aminoglycosides have negligible oral absorption and thus require parenteral administration. They also can be administered directly into body cavities and have a role in the management of pleural and peritoneal infection. Tobramycin is particularly useful for treatment of recurrent *Pseudomonas* infection in patients with cystic fibrosis and can be administered by aerosolized inhalation to facilitate optimal local antimicrobial effect [79]. In a large randomized, placebo-controlled clinical trial involving critically ill adults who had undergone invasive mechanical ventilation, a three-day prophylactic regimen of inhaled amikacin reduced the subsequent incidence of ventilator-associated pneumonia [174]. Neomycin is often used orally as part of a pre-operative bowel decontamination protocol.

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 [15].

Aminoglycosides are excreted unchanged by the kidneys [6]. 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 monitored in all patients with reduced renal function [83].

THE AMINOGLYCOSIDES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Amikacin	5 mg/kg every 8 hrs or 7.5 mg/kg every 12 hrs	15-22.5 mg/kg/day every 8 hrs OR 15-20 mg/kg/dose every 24 hours	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	3-5 mg/kg/day in divided doses every 8 to 12 hrs, or 5-7 mg/kg once daily	Infants: 2-2.5 mg/kg/dose every 6 to 8 hrs	IV, IM, topical		
Neomycin	4-12 g/day in 4 to 6 divided doses for 5 to 6 days, or 4 g/day for an indefinite period	50-100 mg/kg/day in 3 to 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.
Plazomicin	15 mg/kg once daily for 4-7 days	N/A	IV	Renal failure	Boxed warning: Risk factors for nephrotoxicity include pre-existing renal impairment, elderly patients, concomitant. May cause ototoxicity; symptoms may be irreversible and may not become evident until after therapy is complete.
Streptomycin	15-30 mg/kg/day or 1-2 g daily	20-40 mg/kg/day every 6 to 12 hrs in divided doses Max: 1 g/dose or 2 g/day	IM	Renal failure, vestibular nerve damage, auditory nerve damage	This is the most ototoxic of aminoglycosides; levels must be monitored closely. Can cause neuromuscular blockade and respiratory paralysis, especially when given soon after muscle relaxants or anesthesia.
Tobramycin	1-2.5 mg/kg every 8 to 12 hrs. or 4-7 mg/kg once daily dose	<5 yrs: 2.5 mg/kg every 8 hrs >5 yrs: 2-2.5 mg/kg every 8 hrs	IV, IM inhalation solution, ophthalmic ointment or solution	Renal failure, vestibular nerve damage, auditory nerve damage	Effects of nondepolarizing muscle relaxants can be increased. Total body weight (as opposed to ideal body weight) should be used for underweight patients.
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: [6; 16]					Table 4

## TOXICITY

The most common adverse effect associated with aminoglycoside usage is nephrotoxicity, occurring in 10% to 25% of therapeutic courses [84]. Aminoglycosides are freely filtered by the glomeruli and quickly taken up by the proximal tubular epithelial cells, where they exert their main toxic effect by altering phospholipid metabolism. Aminoglycosides also cause renal vasoconstriction [85]. Critical factors in

the development of acute kidney injury secondary to aminoglycoside nephrotoxicity are dosing and duration of therapy. A single daily large dose is preferable to more frequent dosing, as it appears to cause less accumulation in the tubular cells once the saturation point is reached [84]. Additionally, extending the dose interval to more than 24 hours in patients with renal impairment has been found to be effective, with irreversible nephrotoxicity reported in only 1% of patients studied [86].

Vestibular and auditory toxicity may also complicate treatment with aminoglycosides, though this is less common now as clinical awareness and careful dosage adjustment in relation to renal function has improved. These effects are usually reversible, and because there is some data suggesting that there is a genetic predisposition to ototoxicity, this drug class should be avoided in patients who have a family history of ototoxicity with aminoglycosides [87]. When aminoglycoside therapy is expected to exceed five to seven days, baseline testing of auditory function should be performed and monitored weekly for the duration of treatment.

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 disease, due to a curare-like effect on neuromuscular function [88].

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 [89].

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) [6; 90].

## DRUG INTERACTIONS

There are numerous drug interactions that should be taken into consideration when using the aminoglycosides. The risk of nephrotoxicity may be increased with co-administration of other drugs that are nephrotoxic or in patients receiving loop diuretics (e.g., furosemide). Respiratory depression may occur if aminoglycosides are given with nondepolarizing muscle relaxants. Neomycin may affect digoxin levels by altering the bowel flora responsible for the metabolism of digoxin in the GI tract. Gentamicin may also cause increased serum digoxin levels [6; 91].

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 [6].

## SPECIAL POPULATIONS

Amikacin, gentamicin, neomycin, and streptomycin are pregnancy category D due to eighth cranial nerve toxicity that has occurred in the fetus with some aminoglycosides [6]. Plazomicin and tobramycin carry a boxed warning that states pregnant patients should be apprised of potential harm to the fetus with their administration [6].

Traces of amikacin, gentamicin, streptomycin, and tobramycin are excreted in breast milk, but they are compatible with breastfeeding because they are very poorly absorbed from the GI tract [6]. However, they may cause alterations in the normal bowel flora of the infant [6]. It is not known if neomycin or plazomicin are present in breast milk [6].

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 [92]. Geriatric dosing should be based on ideal body weight estimates [6].

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## MACROLIDES

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The original macrolide, erythromycin, was discovered in 1952 by J.M. McGuire. It is produced by *Saccharopolyspora erythraea* (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 [93]. Data challenge the view of macrolides as global inhibitors of protein synthesis. Evidence demonstrates that these agents selectively inhibit the translation of a subset of cellular proteins, that they impact protein synthesis in a context-specific manner, and that they manifest site specificity of action [94; 95; 96; 97; 98].

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 [98; 99; 100].

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 [101]. Lastly, bacterial enzymes have been described that may deactivate erythromycin [102]. 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 [103]. Erythromycin ethylsuccinate and sulfisoxazole are manufactured as suspensions for use in treating acute otitis media in children older than 2 months of age [6]. 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* (when used concomitantly with sulfonamides) 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.

Macrolides are relatively poorly absorbed orally. Fidaxomicin is minimally absorbed and active only locally in the gastrointestinal tract. Food increases absorption of extended-release clarithromycin but has little or no effect on the immediate-release preparation of the drug. Food causes decreased absorption of both azithromycin capsules and erythromycin (including base and stearate formulations) [104]. Erythromycin may also be given intravenously.

All the macrolides have extensive tissue distribution, with less than adequate penetration into the brain tissue and the CSF [104]. Erythromycin is primarily excreted in feces and urine, with 2% to 15% unchanged [6]. Azithromycin is primarily excreted unchanged into the bile. Clarithromycin is excreted in the urine, both unchanged and as the hydroxy metabolite.

It may be necessary to adjust the doses of the macrolides in the presence of severe hepatic insufficiency. Azithromycin should be used with caution in adults with hepatic impairment; no dosage adjustments are recommended for renal impairment [6]. A dosage adjustment of clarithromycin may be appropriate in patients with hepatic impairment and concomitant severe renal impairment; clarithromycin doses may have to be reduced in severe renal failure [6].

THE MACROLIDES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
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 Otitis media: 30 mg/kg as single dose (not to exceed 1,500 mg)	PO, IV, ophthalmic drops	GI upset	One dose of 1 g given PO can be used for non-GC urethritis/cervicitis. Interaction with pimozone/cyclosporine.
Clarithromycin	250–500 mg every 12 hrs, or 1 g/day extended-release formulation for 7 to 14 days	>6 mos of age: 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 or lansoprazole 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, or continuous infusion over 24 hrs (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: 4 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, ophthalmic solution, topical ointment, gel, or pad	GI intolerance (common), phlebitis at IV infusion site	Inhibits liver CYP 450 enzymes 3A4 and 1A2, resulting in multiple significant drug interactions.
Fidaxomicin	200 mg twice daily for 10 days	Not studied in pediatric patients	PO	Nausea, abdominal pain	Used for treatment of diarrhea due to <i>C. difficile</i>
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. Non-GC = nongonococcal infection.					
Source: [6; 16]					Table 5

## SIDE EFFECTS/TOXICITY

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 with eryth-

romycin estolate. 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 [104].



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 [105].

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 [6]. Erythromycin is contraindicated with concurrent use of cisapride, pimozide, dihydroergotamine, ergotamine, lovastatin, simvastatin, astemizole, or terfenadine. Clarithromycin is contraindicated with concurrent use of cisapride, pimozide, ergot alkaloids (e.g., ergotamine), or lomitapide [6]. Serum levels of theophylline, cyclosporine, 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 [6; 106].

Azithromycin is not likely to interact with drugs metabolized by CYP3A4. However, azithromycin interacts with pimozide, potentially resulting in QT interval prolongation and arrhythmia [107]. Co-administration with pimozide is therefore contraindicated. Levels of cyclosporine could potentially be increased and therefore should be monitored closely [6; 108].

## 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. Azithromycin is also category B [6]. The CDC recommends the use of azithromycin for the treatment of *Chlamydia* during pregnancy. Treatment with erythromycin is an approved alternative regimen [109].

Clarithromycin is pregnancy category C, based on the finding that it causes growth retardation in monkeys and adverse effects on other mammals, including fetal loss. A postmarketing surveillance study did not find any evidence of teratogenicity, but a Danish study found a doubling in the frequency of miscarriages among women treated with clarithromycin [110; 111]. The manufacturer recommends that clarithromycin not be used in pregnant women unless there are no alternative therapies [6].

Erythromycin is excreted in breast milk, but the AAP considers it usually compatible with breastfeeding [57]. Clarithromycin is excreted in breast milk, but breastfeeding is considered acceptable when the relative infant dose is less than 10% [112]. One systematic review and meta-analysis demonstrated a significant association between post-natal use of erythromycin and infantile hypertrophic pyloric stenosis [113].

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## QUINOLONES

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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 (fluoroquinolones). As with other classes of synthetic and semisynthetic antimicrobials, alterations of side chains affect antimicrobial activity and pharmacokinetics [114].

## MECHANISM OF ACTION

Quinolones inhibit DNA gyrase and DNA topoisomerase, enzymes that mediate DNA supercoiling, transcription, and repair [6; 115]. Quinolones convert these enzymes into cellular toxins, inhibit replication of bacterial DNA by blocking and/or inhibiting the enzymes, relax DNA supercoils, and enable DNA replication and repair. The interference with replication and transcription processes can lead to permanent chromosomal breaks. If the breaks overwhelm the SOS response and other DNA repair pathways, cell death can occur [116; 117].

Bacterial resistance develops as a result of spontaneous mutations that change the binding sites for quinolones on the DNA gyrase and the DNA topoisomerase [116]. Mutations that decrease the ability of quinolones to cross the cell membrane also occur. Plasmids that carry quinolone resistance genes have been identified as an emerging clinical problem [117; 118].

## PHARMACOKINETICS

The quinolones are active against many gram-positive cocci, gram-negative bacilli, and atypical bacteria (e.g., *Legionella*, *Mycoplasma*). Older quinolones have poor activity against streptococci and anaerobes, at achievable serum levels, is relatively poor, although newer agents, such as moxifloxacin, have better coverage against streptococci (including *S. pneumoniae* with reduced penicillin sensitivity) and some anaerobes [119]. Gram-negative coverage includes *Campylobacter*, *Enterobacter*, *E. coli*, *H. influenzae*, *Klebsiella*, *Salmonella typhi*, *Shigella*, and *Vibrio cholerae* [119]. Indications for the use of quinolones include urinary tract infections, non-gonococcal 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 [6]. The quinolones are absorbed well after oral administration, and peak serum levels in the elderly and those with reduced renal function approximate those achieved with intravenous usage. Food may delay

the time to reach peak serum concentration but does not decrease total absorption. Oral absorption is diminished by coadministration of aluminum, magnesium, calcium, zinc, and/or iron preparations [119]. 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 [6].

Most quinolones are metabolized in the liver and excreted in the urine, reaching high levels in urine. Moxifloxacin is mainly excreted nonrenally. It is metabolized, via glucuronide and sulfate conjugation in the liver, to an inactive metabolite [6; 119; 120]. Ciprofloxacin has a mixed route of elimination. As much as 35% to 70% of the ciprofloxacin dose is excreted renally [6].

In renal insufficiency, the quinolones that are primarily excreted renally and those with mixed routes of elimination require dosage adjustments [6]. Moxifloxacin doses do not have to be adjusted for mild hepatic insufficiency [6].

## SIDE EFFECTS/TOXICITY

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 [6; 121; 122]. 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 [123]. Very rarely, hepatic necrosis and hepatic failure have been reported [6; 124].

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 [125]. Use quinolones with caution in patients with medical problems that predispose the patient to seizures. Quinolones should not be used in patients with CNS disorders [119].

THE QUINOLONES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
Besifloxacin	1 drop 3 times daily (4 to 12 hrs apart) for 7 days	Same as adult dosing	Ophthalmic drops	Headache	Contact lenses should not be worn during treatment
Ciprofloxacin	PO: 250-750 mg every 12 hrs IV: 200-400 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 solution or ointment	GI upset, headache	Photosensitivity can occur. Antacids decrease absorption. Can prolong QT interval. Quinolones may cause tendon inflammation and rupture and may exacerbate myasthenia gravis associated muscle weakness.
Delafloxacin	PO: 450 mg every 12 hrs for 5 to 14 days IV: 300 mg every 12 hrs for 5 to 14 days	Not studied in pediatric patients	PO, IV	GI upset, increased serum transaminases	
Gatifloxacin	Days 1 and 2: 1 drop every 2 hrs while awake Max: 8/day Days 3-7: 1 drop 2 to 4 times/day	>1 yr: same as adult dosing	Ophthalmic drops	Headache, GI upset, conjunctival irritation, keratitis	
Levofloxacin	250-750 mg/day for 5 to 14 days	N/A	PO, IV, ophthalmic drops, inhalation	GI upset, headache, phototoxicity	
Moxifloxacin	400 mg/day for 5 to 14 days	N/A	PO, IV, ophthalmic drops	GI upset, headache	
Ofloxacin	200-400 mg every 12 hrs	N/A	PO, otic, ophthalmic drops	GI upset, headache	
Ozenoxacin	Apply thin layer to affected area (up to 100 cm <sup>2</sup> ) twice/day for 5 days	Infants >2 mos to 12 yrs: Same as adult dosing, except treated area may only be up to 2% of total body surface area (Max: 100 cm <sup>2</sup> ) >12 yrs: same as adult dosing	Topical	<1% experience rosacea-like face eruption, seborrheic dermatitis	
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: [6; 16]					Table 6

There is also a risk of disabling peripheral neuropathy associated with the use of oral or injectable fluoroquinolones [126]. The onset can be rapid, and patients should be advised to contact their health-care provider if any signs or symptoms develop. In these cases, the fluoroquinolone should be stopped and an alternative non-fluoroquinolone drug used, unless the benefit of continued treatment outweighs the risk [119; 126].

In 2018, the FDA strengthened the warnings about the risks of mental health side effects (e.g., disorientation, agitation, delirium) and serious blood sugar disturbances (including hypoglycemia coma) associated with fluoroquinolones [127].

### 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 [119; 128]. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) appears to increase the risk of seizures [6; 129].

Theophylline, phenytoin, and warfarin 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 [6]. Dosage adjustments are not typically needed with other quinolones [119].

### SPECIAL POPULATIONS

Quinolones should be used in pregnancy only if clinical benefit exceeds risk and a safer alternative is not available [119]. Because quinolones enter breast milk, their use during breastfeeding should be avoided if alternative agents are available [119].

Quinolones are not routinely used as first-line therapy for pediatric patients but may be considered a reasonable alternative in situations where no safe and effective substitute is available (e.g., multi-drug resistance) [6].

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## SULFONAMIDES

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Sulfonamides, the first true antibiotics, are derived from azo dyes. The first agent was sulfachrysoidine, used in 1935, which released sulfanilamide *in vivo* [130]. 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 (e.g., prophylaxis for drug-resistant malaria). Some of these agents are no longer available in the United States 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.

Unfortunately, bacterial resistance to sulfonamides is common, with cross-resistance between agents frequently occurring [131]. Mutations that result in additional production of PABA or changes in the enzyme binding sites for sulfonamides are responsible for the resistance [132; 133]. 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 [133; 134].

One method for improving bacterial activity against potentially resistant strains is the addition of trimethoprim [135]. Trimethoprim is a competitive inhibitor of dihydrofolate reductase, another enzyme active in the synthesis of folate [6]. Trimethoprim resistance is also common [136].

## PHARMACOKINETICS

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

### The Short- to Medium-Acting Sulfonamides

This group of agents includes sulfadiazine and sulfamethoxazole. Sulfadiazine is readily diffused into CSF and excreted largely in urine, 15% to 40% as metabolites and 43% to 60% as unchanged drug [6]. It is indicated for use in treating chancroid, trachoma, inclusion conjunctivitis, nocardiosis, UTIs, toxoplasmosis encephalitis, and malaria and for prophylaxis of rheumatic fever [6]. Sulfamethoxazole is combined with trimethoprim and is indicated for *Pneumocystis jiroveci* prophylaxis and treatment, upper respiratory tract infections, and urinary tract infections [6].

### 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 and for juvenile and rheumatoid arthritis in patients who have responded inadequately to salicylates or other NSAIDs [6]. Although absorption of sulfasalazine from the intact intestine is very low, inflammation in the bowel may result in significant absorption of the metabolite sulfapyridine [6].

### Topical Sulfonamides

The topical sulfonamides include mafenide acetate and silver sulfadiazine, which are used in the treatment of burns. Mafenide 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 [6].

## 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 [137].

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.

## SIDE EFFECTS/TOXICITY

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 [131]. Sulfacetamide lotion also contains metabisulfite, which may cause an allergic reaction in patients allergic to sulfites [6].

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 byproduct, (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 crystalluria. Hemolysis is more likely to develop in patients with G6PD deficiency [131].

THE SULFONAMIDES					
Agent	Adult Dosing Range	Pediatric Dosing Range	Route	Common Side Effects	Comments
<b>Short- to Medium-Acting</b>					
Sulfadiazine	2–4 g/day in 3 to 6 divided doses	>2 mos (initial): 75–150 mg/kg/day in 4 to 6 divided doses >2 mos (maintenance): 150 mg/kg/day in 4 to 6 divided doses Max: 6 g/day	PO	Rash, pruritus	Multiple drug interactions. Contraindicated in infants <2 mos of age.
Sulfamethoxazole/trimethoprim (TMP/SMX)	PO: 1–2 DS tablets every 12 to 24 hrs IV: 8–20 mg TMP/kg/day in 2 to 4 divided doses	>2 mos PO: 6–20 mg TMP/kg/day in 2 divided doses IV: 6–20 mg TMP/kg/day every 12 to 24 hours Max single dose: 160 mg TMP/dose	PO, IV	Rash, pruritus	Multiple drug interactions. Weight-based dosing recommendations based on trimethoprim content.
<b>Limited to GI Tract</b>					
Sulfasalazine	RA: Initial: 0.5–1 g every 6 to 8 hrs Maintenance: 2 g/day in divided doses UC: Initial: 3–4 g in evenly divided doses every 8 hours Titrate to 4–6 g in 4 divided doses	>2 yrs: 40–60 mg/kg/day in 3 to 6 divided doses	PO	Anorexia, headache, GI upset	Contraindicated with hypersensitivity to salicylates, sulfasalazine, sulfonamides, or mesalamine.
<b>Topical</b>					
Mafenide	Cream: Apply 1.6 mm thick layer to burn area every 12 or 24 hrs Solution: Wet dressing gauze every 4 hrs or as needed	Use adult dosing	Cream, powder for solution	Burning at application site, rash, allergic reaction	Used for treatment of second- and third-degree burns to prevent infection. Burn area should be covered with cream/wet at all times. Apply with sterile gloved hand.
Silver sulfadiazine	Apply 1.6-mm layer to burn area once or twice daily	Use adult dosing	Cream	Rash, allergic reaction	
Sulfacetamide	Dosage varies with the preparation.	Use adult dosing	Prepared in complex with other topical medications as a solution or ointment	Rash, local irritation	Combinations with fluoro-metholone, prednisolone, and phenylephrine are available, each with differing dosing, indications, and contraindications. Common for ophthalmic and topical 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; RA = rheumatoid arthritis; TMP = trimethoprim; UC = ulcerative colitis.					
Source: [6; 16]					

Table 7

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 [6].

## DRUG INTERACTIONS

Warfarin, phenytoin, and sulfonamides may all be potentiated due to displacement of the drugs from serum albumin by the sulfonamides [6]. Cyclosporine levels may be decreased, and levels should be monitored [6]. 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 [131]. Animal studies with sulfamethoxazole show bone abnormalities and a higher incidence of cleft palate. Adequate studies have not been done in pregnant women [131].

Mafenide, sulfacetamide ophthalmic drops, and sulfadiazine are pregnancy category C. Sulfacetamide lotion has not been studied in pregnancy. Adverse events were not observed in animal reproduction studies of silver sulfadiazine; nevertheless, it is contraindicated for use near term in pregnant women [6].

Sulfonamides are excreted in breast milk. Sulfamethoxazole and sulfisoxazole are considered compatible with breastfeeding by the AAP, although they should be avoided if hyperbilirubinemia or G6PD deficiency is present [57]. Sulfacetamide lotion and silver sulfadiazine have not been studied in breastfeeding but would presumably also be excreted in breast milk; use with caution in breastfeeding women [6]. The manufacturer considers the use of sulfadiazine to be contraindicated in breastfeeding women [6].

Because of the risk of neonatal kernicterus, use of sulfonamides should be avoided in the newborn. Sulfacetamide eye drops have not been studied in children younger than 2 months of age [6].

## 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 (and possibly the 50S ribosomal subunits of susceptible bacteria), blocking the binding of aminoacyl transfer-RNA [6; 138]. 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 [139]. The resistance may be transmitted by plasmids [140].

## MECHANISMS OF ACTION AND PHARMACOKINETICS

The tetracyclines have a broad spectrum of activity that includes aerobic gram-positive and 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 approved by the FDA for treatment of rickettsial infections, typhus, Rocky Mountain spotted fever, trachoma, nongonococcal urethritis, and lymphogranuloma venereum [6].

As a result of decades of clinical and agricultural use, the prevalence of resistance to tetracyclines is now high among common gram-positive and gram-negative pathogens. For this reason, and because they are bacteriostatic, the role of tetracyclines is limited for treatment of most pyogenic infections. Primary indications for this class are atypical infections (e.g. mycoplasma and chlamydia) and zoonoses (e.g. tularemia and brucellosis).

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 [6].

### Short-Acting Tetracyclines

The short-acting tetracyclines include tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. The class previously included oxytetracycline, but the agent is no longer available in the United States [6]. Tetracycline is inexpensive but requires dosing every six hours for most indications. A less frequent dosage protocol is commonly used for the treatment and prevention of acne [6].

### Intermediate-Acting Tetracyclines

The only intermediate-acting agent available in the United States is demeclocycline. Demeclocycline is no longer used as an antibiotic but rather has been used as an off-label drug to treat the syndrome of inappropriate antidiuretic hormone (SIADH) [6; 141]. However, studies have suggested that there is limited high-quality evidence to suggest that demeclocycline is effective in managing this condition, and European clinical practice guidelines recommend against the use of demeclocycline for the management of hyponatremia in patients with SIADH [6; 142].

### Long-Acting Tetracyclines

The long-acting tetracycline agents include doxycycline and minocycline. The main difference between these and the short-acting agents is that these may be dosed less frequently (once or twice daily), which is an advantage in ensuring compliance [6]. 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.

## 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 [6; 143; 144]. The excellent tissue penetration results in the ability of the drug to cross into the dentin, where the tetracycline permanently chelates with the calcium [145].

Most of the tetracycline dose is excreted unchanged into the urine by glomerular filtration, although there is some biliary excretion as well. Nonrenal, possibly hepatic, mechanisms account in large part for excretion of doxycycline and minocycline. Approximately 23% to 40% of doxycycline and 5% to 12% of minocycline is excreted in the urine [6].

Tetracycline should be used with caution in the presence of renal insufficiency, because it accumulates rapidly in the serum in the presence of decreased renal function [6]. Doxycycline may be used in renal failure, as it will be excreted into the bile [6; 146]. Hepatotoxicity has been rarely reported [6].

## SIDE EFFECTS/TOXICITY

Tetracyclines commonly cause GI upset, including nausea, vomiting, and diarrhea. There is conflicting evidence of staining and deformity of the teeth in children younger than 8 years of age. Photosensitivity, idiopathic intracranial hypertension, esophageal ulceration, and hepatotoxicity occur rarely [6].

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 [6]. Minocycline has been associated with a lupus-like reaction [6].

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.



THE TETRACYCLINES					
Agent	Adult Dosing Range	Pediatric Dosing Range <sup>a</sup>	Route	Common Side Effects	Comments
<b>Short-Acting</b>					
Tetracycline	250–500 mg every 6 to 12 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.
<b>Intermediate-Acting</b>					
Demeclocycline	150 mg every 6 hrs or 300 mg every 12 hrs	≥8 years: 8–12 mg/kg/day in 2 to 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.
<b>Long-Acting</b>					
Doxycycline	PO: 100–200 mg/day in 1 to 2 divided doses IV: 100 mg every 12 hrs	<45 kg: 2–5 mg/kg/day in 1 to 2 divided doses Max: 200 mg/day >45 mg: Same as adult dosing	PO, IV	Phlebitis at IV site, photosensitivity, tooth enamel deformities in children <8 yrs of age	Polyvalent cations decrease absorption. Use caution if used with warfarin.
Minocycline	Initial: (IV, PO): 200 mg Maintenance: (IV): 100 mg every 12 hrs Max: 400 mg/day Maintenance (PO): 100 mg every 12 hrs, OR 100–200 mg initially, followed by 50 mg 4 times daily	Initial: (IV, PO): 4 mg/kg/dose Maintenance: 2 mg/kg/dose every 12 hrs Max: 400 mg/day	PO, IV	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. SIADH: syndrome of inappropriate antidiuretic hormone hypersecretion. <sup>a</sup> All pediatric doses are for children older than 8 years of age.					
Source: [6; 16]					

Table 8

## DRUG INTERACTIONS


Several types of drug interactions result in alterations in serum levels of tetracyclines. Agents that alkalinize the urine will increase excretion of the tetracyclines. Polyvalent metal cations (calcium, aluminum, zinc, magnesium, and iron) and bismuth decrease absorption [6; 147]. 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 [6; 148; 149]. The effects of warfarin are increased, probably because tetracyclines depress warfarin metabolism and plasma prothrombin activity, resulting in a synergistic effect [6; 150]. Digoxin effects may be increased because of changes in the bowel flora that are responsible for digoxin metabolism [151].

## SPECIAL POPULATIONS

Tetracycline is 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 [6; 152; 153].

Tetracyclines are excreted into the breast milk in small amounts. Most exposed infants have very low blood levels of the drug and probably are not at risk [6]. In the past, tetracyclines were contraindicated in children younger than 8 years of age because of the risk for tooth deformity. However, doxycycline is the current first-line therapy for Rocky Mountain spotted fever in children of all ages, including those younger than 8 years of age [154]. Limited studies indicate that short courses of the medication were not associated with dental side effects in this population [155].



The Infectious Diseases Society of America asserts that tetracyclines should not be used in children younger than 8 years of age. (https://academic.oup.com/cid/article/52/3/e18/306145. Last accessed January 11, 2024.)

**Level of Evidence:** A-II (Good evidence from >1 well-designed clinical trial, without randomization; cohort or case-controlled analytic studies; multiple time-series; or dramatic results from uncontrolled experiments)

## VANCOMYCIN

Vancomycin is the oldest member of the glycopeptide antibiotics class, a group of large molecules that inhibit bacterial cell wall synthesis. Glycopeptides have a high binding affinity for peptides found only in bacterial cell walls. This interaction disrupts peptidoglycan polymerization, the late-stage reaction that imparts rigidity to the cell wall [6; 156]. Gram-positive organisms, both cocci and bacilli, are highly susceptible to glycopeptides.

Vancomycin was developed more than 50 years ago as an alternative intravenous therapy for serious staphylococcal and streptococcal infections in patients allergic to beta-lactams. In this early period, vancomycin usage was associated with a high incidence of vestibular and renal toxicity. The cause was attributed in large part to impurities in the formulation, a problem solved in subsequent years. At present, the major role for vancomycin is in the treatment of serious infections caused by MRSA, methicillin-resistant *S. epidermidis* (MRSE), and ampicillin-resistant enterococci [157]. An oral formulation is available for the treatment of *C. difficile*-associated diarrhea/colitis.

## MECHANISMS OF ACTION AND PHARMACOKINETICS

Vancomycin is not absorbed by the intestinal tract and must be administered by intravenous infusion, except for the formulation for the treatment of *C. difficile*-associated diarrhea/colitis [6]. The determination of a safe, effective dosage regimen, and decisions regarding monitoring of therapy, are complex matters that require consideration of multiple factors, including the site and severity of infection, the patient's weight and renal function, the susceptibility of the infecting organism, and the anticipated duration of therapy [158]. The usual adult dose is 15–20 mg/kg/dose every 12 hours. The rate of infusion should be no more than 500 mg/hour, as rapid infusion causes an uncomfortable generalized erythroderma (“red man” syndrome) [6]. The red man syndrome is a histamine-mediated flushing that occurs during or immediately following infusion and does not mandate discontinuation unless slowing the infusion rate fails to mitigate the reaction.

## ABSORPTION/ELIMINATION

Vancomycin is cleared almost entirely by the kidneys. Prolonged usage at excessively high therapeutic serum levels has been associated with nephrotoxicity and ototoxicity [6]. In treating patients with invasive staphylococcal infection and MRSA, it is considered important to use the maximum dosage (target trough serum vancomycin level of 15–20 mcg/mL) in order to assure optimal therapeutic effect [158]. The serum creatinine and trough vancomycin level (target <20 mcg/mL) should be monitored once or twice weekly in such cases, as well as in all patients who are elderly or have impaired renal function.

## SIDE EFFECTS/TOXICITY

Apart from the (avoidable) red man syndrome, vancomycin administration is well tolerated and side effects are uncommon. As with beta-lactams and sulfonamides, vancomycin is a good sensitizing agent; allergic manifestations such as fixed drug eruptions and drug fever are relatively common. Vancomycin nephrotoxicity does occur. The incidence is low, the exact mechanism is poorly understood, and the impact is usually reversible upon discontinuation of the drug. Risk factors for nephrotoxicity include total daily dose in excess of 3–4 grams, trough serum vancomycin levels >20 mcg/mL, pre-existing renal disease, concomitant use of other nephrotoxic drugs (e.g. aminoglycosides), and duration of therapy longer than one week [159].

In 2017, the FDA published a safety review that indicated that use of intraocular vancomycin prophylactically during cataract surgery, alone or in a compound formula, should be avoided because of the risk of hemorrhagic occlusive retinal vasculitis [6; 160].

Reversible neutropenia, presumably from bone marrow toxicity, is sometimes seen in patients receiving prolonged vancomycin therapy (e.g., for endocarditis and osteomyelitis). Oral vancomycin is not absorbed and thus imposes no risk of nephrotoxicity or ototoxicity.

## ANTIMICROBIAL PEPTIDES

The increasing prevalence of antimicrobial resistance among clinical isolates of staphylococci and streptococci severely limits therapeutics for serious infections caused by these common pathogens. Thus, there is ongoing research on alternative antimicrobial mechanisms and development of novel therapies needed for treatment of multidrug-resistant bacterial infection. Antimicrobial peptides are naturally occurring molecules and semisynthetic derivatives that have bactericidal activity against micro-organisms. Naturally occurring peptides with antimicrobial activity are produced by a variety of organisms (e.g., plants, insects, marine life) and serve to protect the host from pathogenic micro-organisms. Antimicrobial peptides exert their effects via multiple mechanisms: cell-membrane attachment, disruption, and leakage of cell contents; inhibition of intracellular protein and nucleic acid synthesis; attenuation of protein folding; and prevention of cell wall biosynthesis [175].

## DAPTOMYCIN

Daptomycin is a cyclic lipopeptide produced by *Streptomyces roseosporus* having bactericidal activity against a wide range of gram-positive cocci. The spectrum of activity includes human pathogens such as methicillin-sensitive *Staphylococcus aureus*, MRSA, and *Enterococcus*. The exact mechanism of action is unclear; it targets the bacterial cell membrane where interactions lead to rapid depolarization due to potassium efflux, leakage of cell contents, and disruption of the architecture of the cell membrane [175]. Following clinical trials to assess efficacy and the parameters of safe dosage, daptomycin was approved by the FDA in 2006 for parenteral treatment (4 mg once daily) of complicated bacterial skin and soft tissue infections. Subsequent experience and formal clinical trials have demonstrated that daptomycin efficacy is comparable to standard therapy for treatment of MRSA bacteremia and endocarditis, especially when administered at the

higher dose of 6–10 mg daily. Daptomycin is an option for salvage and first-line treatment of bacteremia, endocarditis, and osteomyelitis caused by MRSA and Enterococcus isolates showing resistance to vancomycin (minimal inhibitory concentration >2 mg/L) [176].

Adverse effects of daptomycin are rare with once daily dosing. Skeletal myopathy has been reported, mostly prior to 2006 when daptomycin was administered in multiple daily doses. When high dosage or prolonged daptomycin regimens are employed, coadministration with other drugs associated with myopathy, such as hydroxymethylglutaryl CoA reductase inhibitors (statins), should be avoided, and patients should be monitored for muscle pain or weakness [177]. Eosinophilic pneumonia has been reported in association with prolonged treatment of osteomyelitis. In a cohort study involving 1,021 patients who received daptomycin for bone and joint infections, 17 (1.7%) were diagnosed with daptomycin-induced eosinophilic pneumonia [178]. All patients recovered upon discontinuation of daptomycin.

## LYPOGLYCOPEPTIDES

Lipoglycopeptides are semisynthetic derivatives of glycopeptides, akin to vancomycin and developed for treatment of multidrug-resistant staphylococcal and enterococcal infections. These newer agents have enhanced activity and favorable pharmacokinetics—in some cases, permitting administered at weekly intervals. In comparison to vancomycin, lipoglycopeptides have greater potency against gram-positive bacteria, including vancomycin-resistant strains, and appear less likely to lead to emergence of resistant organisms [161; 162; 179]. As with vancomycin, lipoglycopeptides must be administered intravenously. The lipophilic side chain prolongs plasma half-life and helps anchor these agents to the outer structure of the bacterial cell, inhibiting cell wall synthesis and disrupting cell membrane integrity [163]. In animal studies, lipoglycopeptides have proven effective in treating a variety of serious gram-positive infections, including bacteremia, pneumonia, and endocarditis [161; 162]. Clinical studies of efficacy in humans have been limited to date.

At present, three lipoglycopeptides, telavancin, dalbavancin, and oritavancin, are approved by the FDA for the treatment of acute bacterial skin and soft-tissue infection. Clinical trials show equivalent or superior efficacy against MRSA skin infection when compared with vancomycin [7; 162; 164]. Telavancin is also approved for treatment of hospital-acquired and ventilator-associated *S. aureus* pneumonia. A phase III clinical trial is ongoing to assess telavancin efficacy and safety for treatment of complicated *S. aureus* bacteremia and right-sided endocarditis [179]. The side effect profile of these agents is mild and comparable to other effective regimens. Reported adverse effects include headache, nausea, pruritus, pain at injection site, and fever. Taste disturbance (i.e., metallic taste), nausea and vomiting, and foamy urine have been reported with telavancin [6; 163].

Of note, a risk/benefit analysis should be conducted when using telavancin in patients with pre-existing moderate-to-severe renal impairment treated for hospital-acquired or ventilator-associated bacterial pneumonia, as mortality is increased compared with administration of vancomycin [6].

Dalbavancin has the advantage of a prolonged plasma half-life (6 to 10 days), allowing for weekly administration and perhaps obviating the need for an indwelling central line. In adults and children 12 to 17 years of age, the best-studied treatment protocol is 1 g IV, followed by 500 mg weekly [164; 165]. In a randomized trial comparing dalbavancin (1 g IV on days 1 and 8) with vancomycin (IV for 3 days followed by the option of oral linezolid to complete 10 to 14 days) for treatment of skin infection, the clinical response outcomes were similar in both treatment arms. For patients with *S. aureus* infection, including MRSA, clinical success was observed in 90.6% of patients treated with dalbavancin and 93.8% of those who received vancomycin-linezolid [164].

The lipoglycopeptides have had some adverse effects on fetal development in animals; safety data in pregnant women are limited. These agents should be used during pregnancy only when the benefit outweighs the risk [163].

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## PLEUROMUTILINS

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Pleuromutilins were discovered as natural-product antibiotics in 1950. However, their use was limited to veterinary medicine until 2007, when the first agent (retapamulin) was approved for use in humans [166]. Retapamulin was only approved for topical application. In 2019, lefamulin was approved for human use via oral and intravenous delivery [6]. Pleuromutilin derivatives are designed primarily through modifications at the C(14) side chain [166].

These agents inhibit bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and Van der Waals forces) with the A- and P-sites of the peptidyl transferase center in domain V of the 23s ribosomal RNA of the 50S subunit [6]. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents correct positioning of transfer RNA [6].

Retapamulin is used for the topical treatment of impetigo. A small amount is applied to the affected area twice per day for five days [6]. Possible side effects include eczema, application site reactions, diarrhea, headache, and nasopharyngitis.

Lefamulin is approved for the treatment of community-acquired bacterial pneumonia [6; 167]. The usual dose is 600 mg every 12 hours for oral administration or 150 mg every 12 hours for IV use [6]. Treatment is generally at least five days; patients should be afebrile for  $\geq 48$  hours and clinically stable prior to discontinuation. The most common adverse reactions include diarrhea, nausea, injection site reactions, elevated liver enzymes, and vomiting [167]. It is contraindicated in patients with certain arrhythmias or who are prescribed drugs to prolong QT intervals.

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## INVESTIGATIONAL ANTIBIOTICS FOR DRUG-RESISTANT MICRO-ORGANISMS

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Researchers continue to explore new methods and the search for drugs to aid in the prevention of antibiotic resistance. Progress has been made in recent years, with two new antibiotics void of cross-resistance with existing antibiotics being discovered through soil sample screening: teixobactin and pseudouridimycin.

Teixobactin, a cyclic depsipeptide antibiotic, works by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid), inhibiting bacterial cell wall biosynthesis [168; 169]. Teixobactin has been shown effective at treating an array of gram-positive pathogens, including MRSA, vancomycin-resistant *Enterococcus*, and *Mycobacterium tuberculosis*, with no known cross-resistance to other antibiotics [168; 169]. With reports in 2016 of efficient syntheses of two teixobactin analogues, this class of drugs may be part of the solution to bacteria resistant to currently available antibiotics [168; 169].

Pseudouridimycin, a nucleoside-analog inhibitor, acts by inhibiting bacterial RNA polymerase, an enzyme responsible for bacterial RNA synthesis, through a binding site. The structure is similar to rifampin, an antitubercular agent that inhibits the enzyme; however, the mechanism of action does differ so as not to cause a cross-reaction with rifampin [170; 171]. Pseudouridimycin has been shown effective for a broad spectrum of drug-sensitive and drug-resistant bacteria.

Researchers are currently attempting to conduct synthesis of these two new classes of drugs with varying, but promising, success. Although it may take several years for these or other new antibiotics with no cross-resistance to be developed, promising progress is continuing, and researchers estimate that, once approved, resistance to these novel drugs could take decades, rather than years, to develop [168; 169; 170; 171].

## CONCLUSION

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Antibiotics are commonly used drugs that have diverse actions, side effects, and toxicities. The large number of antibiotics available makes it challenging to understand the important characteristics of each antimicrobial class, including clinical indications, spectrum of activity, dosage, and toxicities. Knowing the general characteristics by antibiotic class and having experience with one or two key agents within each class improves recall and facilitates the selection of the most appropriate antibiotic for a given bacterial infection.

An understanding of the mode of action, spectrum of activity, and potential toxicity enables the practitioner to tailor a therapeutic regimen specific to the infectious etiology and of appropriate duration. This in turn lessens the likelihood developing microbial resistances and reduces risk of adverse effects.

It is important to remember that the indications given by the FDA are guidelines. Many antibiotics are used for off-label purposes, and occasionally in doses that differ from those recommended for the usual indications. This may be necessary when faced with managing severe and life-threatening infections or for special populations, such as premature infants, neonates, and the elderly. Before using a specific agent, one should always consider carefully reviewing the detailed information (package insert) provided by the manufacturer.

### Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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### **Evidence-Based Practice Recommendations Citations**

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