Antibiotics Review

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, Florida nurse, or CST/CSFA, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

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 Planners
John M. Leonard, MD
Jane C. Norman, RN, MSN, CNE, PhD
Abimbola Farinde, PharmD, PhD
Shannon E. Smith, MHSC, CST, CSFA

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

Audience
This course is designed for healthcare providers who prescribe and administer antibiotics to patients, including physicians, physician assistants, pharmacists, pharmacy technicians, nurses, nurse practitioners, and surgical technologists and assistants.

Accreditations & Approvals

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Designations of Credit
NetCE designates this enduring material for a maximum of 5 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 5 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to satisfy the Lifelong Learning requirement for the American Board of Ophthalmology's Maintenance of Certification program. It is the CME activity provider's responsibility to submit learning completion information to ACCME for the purpose of granting MOC credit.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may

A complete Works Cited list begins on page 39.

Mention of commercial products does not indicate endorsement.

record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 5 ANCC contact hours.

This activity was planned by and for the healthcare team, and learners will receive 5 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 6 hours for Alabama nurses.

NetCE designates this continuing education activity for 5 pharmacotherapeutic/pharmacology contact hours.

AACN Synergy CERP Category A.

NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-19-006-H01-P and JA4008164-0000-19-006-H01-T.

This continuing education activity is approved for 8.5 CE credits by the Association of Surgical Technologists, Inc., for continuing education for the Certified Surgical Technologist, Certified Surgical First Assistant, and Associate members of AST. This recognition does not imply that AST approves or endorses any product or products that are included in enduring materials.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 11/21/2021); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2021); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

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 anti-microbial resistant strains within the healthcare environment.
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.

Pharmacy Technician Learning Objectives

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

1. Outline the general characteristics and mode of action of antibiotics commonly in use.
2. Describe practices to limit the emergence and transmission of antimicrobial resistant strains of bacteria.
3. Compare and contrast agents from the various classes of antibiotics.

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 and the newer glycopeptide analogues is also included.

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

According to the Centers for Disease Control and Prevention, administration of currently available probiotics is not recommended to prevent primary *Clostridium difficile* infection, as there are limited data to support this approach and there is a potential risk of bloodstream infection.

(https://www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSA-SHEA-CDI-guidelines-2010.pdf. Last accessed January 22, 2018.)

Level of Evidence: CIII (Poor evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)

ANTIBIOTIC RESISTANCE

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 million people become infected with bacteria that are resistant to antibiotics, and approximately 23,000 people die annually because of these infections [164]. 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 [2].

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 [3].

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 a large number of nearby bacteria, which may or may not be the same species. In this manner, resistance can quickly spread from species to species [4].

Many strategies have been used in an attempt to circumvent the multiple mechanisms of resistance encountered in bacteria. Among these are the 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 pairing two drugs to enhance the antimicrobial effect (e.g. sulfamethoxazole with trimethoprim).

In addition, new categories of antibiotics are being created in an attempt 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 methicillin-resistant *Staphylococcus aureus* [149; 171]. Nonetheless, development of resistance in bacteria is relentless.

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

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

The next step is to tailor medical treatment to fit the infection. Antimicrobial therapy should be based on the likely pathogens or results of culture, so broad-spectrum antibiotics may be avoided when possible. Consideration should be given to pathogens common to the area of infection (e.g., skin, intra-abdominal) and to pathogens common in the environment locally (e.g., hospital environment). Prolonged treatment regimens increase the likelihood of emerging resistance, so the duration of therapy should be carefully monitored and undue prolongation avoided.

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

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.

(http://www.cochrane.org/CD003543/EPOC_improving-how-physicians-working-hospital-settings-prescribe-antibiotics. Last accessed January 22, 2018.)

Level of Evidence: Meta-analysis

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

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

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

PENICILLINS

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 [150].

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 [6]. Although the exact mechanisms involved are not known, the end result is that the cell wall is structurally weakened and lyses, leading to cell death.

The basic form of penicillin is structured around the beta-lactam ring (a thiazolidine ring) and can be altered by substituting side chains. By doing so, the antimicrobial spectrum, absorption characteristics, and resistance to beta-lactamase deactivation can be 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 [7]. In addition, some bacteria are able to prevent binding to the PBPs by various means, including altered binding sites for the penicillins [8].

Various strategies have been employed to circumvent these microbial adaptations. Altering the structure of the 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. 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 [9].

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. They 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 [149].

THE PENICILLINS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Natural Penicillins					
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: O.6 MU 14 to 27 kg: 1.2 MU in one dose	IM	Rash, GI upset	
Penicillin G (parenteral/ aqueous)	12–24 MU per day	100,000–300,000 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	—
Aminopenicillins					
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.
Penicillinase-Resistant Penicillins					
Dicloxacillin	125–500 mg every 6 hrs	<40 kg: 12.5–25 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.
Antipseudomonal Penicillins					
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: [148; 149] *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 [149]. 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 [149].

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 [149].

While the penicillinase-resistant penicillins are effective against many of the same gram-positive organisms that the natural penicillins are effective against, 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 was oral, are no longer available in the United States.

These agents retain much of their activity against gram-positive bacteria, but they also have more activity against gram-negative bacteria, including *Pseudomonas aeruginosa*. Additional gram-negative species that are treated by these agents include *H. influenzae*, *Serratia* species, and *Klebsiella* species.

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 [10].

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.

Once absorbed, these agents are widely distributed throughout the body. Therapeutic concentrations of penicillins are readily achieved in tissues and secretions (e.g., joint fluid, pleural fluid, pericardial fluid, and bile). Low concentrations are found in prostatic secretions, brain tissue, intraocular fluid, and phagocytes. Cerebrospinal fluid (CSF) concentrations vary but are less than 1% of serum concentration when the meninges are normal.

When the meninges are inflamed, CSF concentrations may rise to 5% and can be increased by co-administration of probenecid (500 mg 4 times daily) [11; 149]. 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 of the penicillins are excreted to some degree in the bile, but biliary excretion is most important for antipseudomonal penicillins and nafcillin [12].

In patients with mild renal insufficiency, dosage adjustment is not needed, except with the use of ticarcillin [13]. If the creatinine clearance is less than 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 [165; 166; 167; 168]. 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 percentage 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% [14; 165; 166; 167]. 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 [165; 167; 168]. 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 [12; 149]. 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) [149]. 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 [165; 166; 167].

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

DRUG INTERACTIONS

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

SPECIAL POPULATIONS

The penicillins are pregnancy category B, indicating no adverse events noted in animal studies [17]. These agents are secreted in breast milk, and breastfeeding should be avoided if the infant is allergic to any of the penicillins [18]. Use while breastfeeding may cause modifications of normal intestinal flora and allergic sensitization in the infant [149].

CEPHALOSPORINS

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 [19].

MECHANISM OF ACTION

Like penicillins, the cephalosporins are beta-lactams in which the beta-lactam ring is joined to a dihydrothiazine ring. Their antimicrobial effect is based on the same mechanism of action 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 [20; 21].

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

As with penicillins, resistance to the action of cephalosporins 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 [22]. An additional source of resistance in gram-negative bacteria is alteration in the cell-membrane porins that normally allow passage of the cephalosporins [23].

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

PHARMACOKINETICS

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

First-Generation Cephalosporins

The first-generation cephalosporins are most active against aerobic gram-positive cocci. These agents include cefazolin, cephalexin, 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**
1st Generation					
Cefadroxil	1–2 g/day in 2 divided doses	30 mg/kg/day in 2 divided doses Max: 2 g/day	PO	Rash, diarrhea	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.
2nd Generation					
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.
3rd Generation					
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**
3rd Generation *(Continued)*					
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.
4th Generation					
Cefepime	IV: 1–2 g every 8 to 12 hrs IM: 0.5–1 g every 12 hrs	IV, IM: 50 mg/kg every 8 to 12 hrs Not to exceed adult dosing	IV, IM	Phlebitis at infusion site, GI upset	Can interfere with some urine glucose tests.
5th Generation					
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.
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: [148; 149]					*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) [25].

Fourth-Generation Cephalosporins

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

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. As with other beta-lactams, ceftaroline exerts its antimicrobial affect 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* [152]. 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 [153]. 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 [154].

ABSORPTION/ELIMINATION

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

The presence of food or antacids may increase or decrease the absorption, depending on the drug. Cefuroxime axetil and cefpodoxime proxetil have increased absorption when taken with food. Cefaclor, cefadroxil, 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 H2 antagonists [27].

There is extensive distribution of the cephalosporins into body tissues and fluids. They readily cross the placenta and are also found in synovial fluid. Concentrations in bile and urine are high. Most cephalosporins do not cross into the CSF in sufficient concentration to be recommended for the treatment of meningitis, but there are some exceptions. Cefuroxime, cefotaxime, ceftriaxone, cefepime, and ceftaroline all have good penetration into the CSF [28; 152].

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

In severe hepatic insufficiency, compensatory changes in renal excretion of the hepatically metabolized drugs may occur [29]. 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 [30]. The most common complaints are GI upset, resulting in nausea, vomiting, or diarrhea. Thrombophlebitis can occur with intravenous (IV) administration. One to three percent of patients develop an allergic reaction. Rash, fever, eosinophilia, and urticaria can develop. Anaphylaxis is rare. Infrequently, there is some cross-sensitivity with true penicillin allergy (estimated nearly 0%to 10% of cases); this occurs mostly with first-generation cephalosporins [13; 165; 166; 167]. 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 [31]. 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 the bile [32]. Rare reactions include hematologic toxicity with resultant eosinophilia, thrombocytopenia, and leukopenia, all of which resolve after stopping treatment [33]. Rarely, hemolytic anemia develops [34]. Hypoprothrombinemia may occur with cephalosporins with the MTT side chain as a result of interference by the MTT moiety with the synthesis of vitamin-K-dependent clotting factors [35]. For patients at high risk of bleeding, exogenous vitamin K may help alleviate this side effect. False-positive glucosuria testing with a copper reduction test (Clinitest) may occur with many cephalosporins [36].

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.

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 [37; 38].

CARBAPENEMS

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

MECHANISM OF ACTION

Like other beta-lactams, the carbapenems inhibit mucopeptide synthesis in the bacterial cell wall by binding to PBPs, leading to lysis and cell death. Bacterial resistance may occur due to a specific beta-lactamase that affects carbapenems. Another significant source of resistance is a mutation that results in the absence of the outer membrane porin, thus not allowing transport of the drug into the cell [40]. Cross-resistance may occur between the carbapenems.

PHARMACOKINETICS

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

Imipenem and ertapenem are approved by the FDA for use in urinary tract infections, pneumonia, intra-abdominal infections, and skin and soft-tissue infections [149]. Meropenem is approved by the FDA for treatment of intra-abdominal infections, skin and skin structure infections, and meningitis in patients older than 3 months of age [149]. Combination meropenem/vaborbactam is approved for the treatment of complicated urinary tract infections caused by susceptible micro-organisms [163].

ABSORPTION/ELIMINATION

Imipenem/cilastatin, meropenem, and ertapenem are given parenterally, as they are unstable in stomach acid. Imipenem is combined with cilastatin, which inhibits dehydropeptidase I in the proximal renal tubular cells. Dehydropeptidase I inactivates imipenem by 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 [42]. Meropenem, doripenem, and ertapenem do not require a dehydropeptidase I inhibitor.

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

Most of the imipenem/cilastatin dose is excreted in the urine. The remaining 20% to 25% of the dose is excreted through an unknown mechanism. Meropenem is excreted unchanged into the urine by means of glomerular filtration and tubular secretion [44]. Ertapenem is metabolized by hydrolysis of the beta-lactam ring, and then both the metabolite and parent drug are excreted in the urine.

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

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 [45]. Hypersensitivity reactions may occur, and while there is a degree of cross-sensitivity with penicillins, this risk is lower than previously believed [165; 166; 167]. Carbapenems should be used with caution in patients allergic to the carbapenems or penicillins.

DRUG INTERACTIONS

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

SPECIAL POPULATIONS

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

The safety of 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 [49]. 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 [50]. Aztreonam is the only available example of this class of drugs. Aztreonam was originally extracted from *Chromobacterium violaceum*. It is now manufactured as a synthetic antibiotic.

MECHANISM OF ACTION

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

PHARMACOKINETICS

Aztreonam does not have significant activity against gram-positive or anaerobic bacteria and is primarily used 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 [51]. Aztreonam is mainly excreted in the urine as an unchanged drug, although there is also minimal hepatic metabolism [52]. Doses must be adjusted for renal insufficiency based on glomerular filtration rate [53].

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 [54].

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

DRUG INTERACTIONS

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

SPECIAL POPULATIONS

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

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

Aztreonam has not been studied for use in children younger than 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 [149]. It has been shown to be very useful in children with respiratory symptoms of cystic fibrosis [58].

THE OTHER BETA-LACTAMS					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Carbapenems					
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.
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: [148; 149]					*Table 3*

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 [59].

Although resistance to aminoglycosides is less common than with many other antibiotics, it can develop as a result of three known mechanisms. The most common pattern of resistance 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 [60].

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

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

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		
Kanamycin	5–7.5 mg/kg/day divided every 8 to 12 hrs Max: 1.5 g/day	15 mg/kg/day in 2 to 3 divided doses	IV, IM[a]		
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.
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	IV, 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.
[a]IM formulation no longer available in the United States.

Source: [148; 149] *Table 4*

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, amikacin, and kanamycin. 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 [58]. 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 [9].

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

TOXICITY

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

Less commonly, vestibular and auditory impairment may develop during treatment with aminoglycosides. These effects are usually reversible, and because there is some data suggesting that there is a genetic predisposition to ototoxicity, this drug class should be avoided in patients who have a family history of ototoxicity with aminoglycosides [66]. 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 [67].

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

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

DRUG INTERACTIONS

There are numerous drug interactions that should be taken into consideration when using the aminoglycosides. 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 [69].

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

SPECIAL POPULATIONS

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

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

Half-life alterations occur in patients at extremes of age. The half-life in neonates and low-birth-weight infants may be considerably prolonged. The elderly may also have a longer aminoglycoside half-life due to an age-related decrease in renal function [62]. Geriatric dosing should be based on ideal body weight estimates [149].

MACROLIDES AND TELITHROMYCIN

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 [72].

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

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

of the erythromycin. Lastly, bacterial enzymes have been described that may deactivate erythromycin [75]. It is likely that this form of resistance is also transferred on plasmids.

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

PHARMACOKINETICS

Erythromycin has a wide spectrum of activity. Gram-positive bacteria that are usually susceptible to erythromycin include the *Streptococcus* species. Erythromycin is a second-line agent for gram-negative bacteria, such as *H. influenzae* and *M. catarrhalis*. Macrolides are particularly useful for their coverage of atypical bacteria, such as *Mycoplasma* and *Chlamydia*. Some spirochetes and mycobacteria are also susceptible to the macrolides. These drugs are indicated for upper respiratory tract infections, such as sinusitis, otitis media, pharyngitis, and bronchitis. They are also useful in the treatment of pertussis, Legionnaires disease, and diphtheria. Telithromycin, which has a long half-life and can be given once daily, has proved useful for the management of community-acquired pneumonia [149]. However, in 2016, the manufacturer of telithromycin announced the discontinuation of the drug [149].

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

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

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

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

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. There have also been some reports of reversible hearing loss in patients treated with erythromycin in high doses or in the presence of renal insufficiency. With IV erythromycin, prolongation of the QT interval and ventricular tachycardia may occur [82].

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

THE MACROLIDES AND TELITHROMYCIN					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Macrolides					
Azithromycin	PO: 250–600 mg/day, or 1–2 g/day IV: 250–500 mg/day	PO: 5–12 mg/kg/day Max: 500 mg/day 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 pimozide/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 is one regimen used for *H. pylori* 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 *C. difficile*
Ketolides					
Telithromycin[a]	800 mg every 24 hrs for 7 to 10 days	Not studied for children <13 yrs of age >13 yrs: Use adult dosing	PO	Nausea, diarrhea	Occasionally causes visual changes (reversible). Inhibits liver CYP 450 enzyme 3A4, resulting in multiple significant drug interactions. Cases of serious or fatal respiratory failure have occurred in patients with myasthenia gravis.

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.
[a]Drug discontinued by manufacturer in 2016.

Source: [148; 149] *Table 5*

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

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

DRUG INTERACTIONS

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

Azithromycin is not likely to interact with drugs metabolized by CYP3A4. However, azithromycin interacts with pimozide, potentially resulting in QT interval prolongation and arrhythmia [87]. Co-administration with pimozide is therefore contraindicated. Levels of cyclosporine could potentially be increased and therefore should be monitored closely [88].

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

SPECIAL POPULATIONS

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

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

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

QUINOLONES

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

MECHANISM OF ACTION

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

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

PHARMACOKINETICS

The quinolones are active against many gram-positive cocci, gram-negative bacilli, and atypical bacteria (e.g., *Legionella*, *Mycoplasma*). Quinolone activity against streptococci and anaerobes, at achievable serum levels, is relatively poor, although newer agents, such as moxifloxacin, have better coverage for anaerobes [99]. Gram-negative coverage includes *Campylobacter*, *Enterobacter*, *E. coli*, *H. influenzae*, *Klebsiella*, *Salmonella typhi*, *Shigella*, and *Vibrio cholerae*. Indications for the use of quinolones include urinary tract infections, 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. 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. The drugs are distributed well throughout all tissues, including the prostate, although the levels in the CSF and prostatic fluid are lower than serum levels [100].

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

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

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

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: 45 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		
Gatifloxacin	Day 1: 1 drop every 2 hrs while awake Max: 8/day Days 2–7: 1 drop 2 to 4 times/day	>1 yr: same as adult dosing	Ophthalmic drops	Headache, GI upset, conjunctival irritation, keratitis	
Gemifloxacin[a]	320 mg once daily for 5 to 7 days	N/A	PO	GI upset, headache, rash	
Levofloxacin	250–750 mg/day for 5 to 14 days	N/A	PO, IV, ophthmalmic drops, inhalation	GI upset, headache, phototoxicity	
Moxifloxacin	400 mg/day for 5 to 14 days	N/A	PO, IV, ophthalmic drops	GI upset, headache	
Norfloxacin[a]	400 mg every 12 hrs, or 800 mg as a single dose for GC	N/A	PO	GI upset, headache	Antacids decrease absorption.
Ofloxacin	200–400 mg every 12 hrs	N/A	PO, otic, ophthalmic drops		
Ozenoxacin	Apply thin layer to affected area (up to 100 cm^2) 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^2) >12 yrs: same as adult dosing	Topical	<1% experience rosacea-like face eruption, seborrheic dermatitis	Novel drug for treatment of impetigo caused by *Staphylococcus aureus* or *Streptococcus pyogenes*

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.
[a]No longer available in the United States.

Source: [148; 149] *Table 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 [104; 105]. Rarely, hematologic toxicities have occurred, resulting in hemolytic anemia (more likely to occur in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency), aplastic anemia, and agranulocytosis [106]. Very rarely, hepatic necrosis and hepatic failure have been reported [107].

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

There is also a risk of disabling peripheral neuropathy associated with the use of oral or injectable fluoroquinolones [155]. The onset can be rapid, and patients should be advised to contact their healthcare 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 [155].

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 hypoglycemic coma) associated with fluoroquinolones [176].

DRUG INTERACTIONS

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

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

SPECIAL POPULATIONS

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

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

SULFONAMIDES

Sulfonamides, the first true antibiotics, are derived from azo dyes. The first agent was sulfachrysoidine, used in 1935, which released sulfanilamide in vivo [115]. Modifications were made to the sulfanilamide to reduce side effects, resulting in the development of the modern sulfonamides. Many of the sulfonamides are no longer used as parenteral agents, but they continue to be used as topical agents or for treatment in specific conditions (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. Mutations that result in additional production of PABA or changes in the enzyme binding sites for sulfonamides are responsible for the resistance [116]. Genes for these resistant mutations may be carried on plasmids, allowing rapid transfer to other similar bacteria and resulting in more rapid development of resistance patterns than through random mutation alone [117].

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

PHARMACOKINETICS

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

The Short- to Medium-Acting Sulfonamides

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

The Long-Acting Sulfonamides

The long-acting agents have been associated with severe allergic reactions and for the most part been replaced in use by the less-toxic sulfonamides. The last long-acting agent available in the United States was sulfadoxine, which is given as a combination with pyrimethamine; however, as of 2018, this agent is no longer available. This drug was reserved for the treatment of drug-resistant malaria and certain cases of *Toxoplasma gondii* infestation. Pyrimethamine inhibits dihydrofolate reductase in *Plasmodium* species during the erythrocytic stage [149].

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

Sulfonamides Limited to Gastrointestinal Tract Activity

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

THE SULFONAMIDES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
Short- to Medium-Acting					
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	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.
Long-Acting					
Sulfadoxine/ pyrimethamine[a]	Single dose of 3 tablets (total: sulfadoxine 1,500 mg and pyrimethamine 75 mg)	Weight-based dosing: Sulfadoxine 25–70 mg/kg and pyrimethamine 1.25–3.5 mg/kg as a single dose	PO	Folic acid deficiency, blood dyscrasias, GI upset	For malaria prophylaxis: A single dose should be carried for self-treatment in the event of febrile illness when medical attention is not immediately available. Note: Discontinue at first sign of rash, myelosuppression, or active bacterial/fungal infection.
Limited to GI Tract					
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.
Topical					
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	

Table 7 continues on next page.

THE SULFONAMIDES *(Continued)*					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range**	**Route**	**Common Side Effects**	**Comments**
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 fluorometholone, 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. [a]Not currently available in the United States.					
Source: [148; 149]					*Table 7*

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 [149].

ABSORPTION/ELIMINATION

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

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

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

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

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

Less common reactions include metabolic acidosis that may occur with absorption of mafenide due to a 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 [123]. Hemolysis is more likely to develop in patients with G6PD deficiency [124].

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

DRUG INTERACTIONS

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

SPECIAL POPULATIONS

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

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

Sulfonamides are excreted in 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 [38]. 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 [149].

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 [149].

TETRACYCLINES

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

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

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

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 [149].

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 [149].

Short-Acting Tetracyclines

The short-acting tetracyclines include oxytetracycline and tetracycline, the namesake of the class. Frequent dosing is needed because of the very short half-life of these agents. Oxytetracycline is no longer available in the United States [149]. Tetracycline 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 [149].

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) [132]. 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 [149; 169].

Long-Acting Tetracyclines

The long-acting tetracycline agents, doxycycline and minocycline, are the more recently developed drugs. The main difference between these and the short-acting agents is that these may be dosed less frequently (once or twice daily), which is an advantage in ensuring compliance. 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 [133; 134]. The excellent tissue penetration results in the ability of the drug to cross into the dentin, where the tetracycline permanently chelates with the calcium [135].

Most of the tetracycline dose is excreted unchanged into the urine by glomerular filtration, although there is some biliary excretion as well. Nonrenal, possibly hepatic, mechanisms account in large part for excretion of doxycycline and minocycline. Only 20% to 26% of doxycycline and 4% to 19% of minocycline is excreted in the urine [136].

Tetracycline should be avoided in the presence of renal insufficiency, because it accumulates rapidly in the serum in the presence of decreased renal function. Doxycycline may be used in renal failure, as it will be excreted into the bile [137]. Because tetracyclines have been known to cause hepatic toxicity, they should not be used in patients with hepatic insufficiency [138].

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 [149].

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

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

THE TETRACYCLINES					
Agent	**Adult Dosing Range**	**Pediatric Dosing Range[a]**	**Route**	**Common Side Effects**	**Comments**
Short-Acting					
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.
Intermediate-Acting					
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.
Long-Acting					
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.
[a]All pediatric doses are for children older than 8 years of age.

Source: [148; 149] *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 [141]. Drugs that induce hepatic enzymes may decrease the half-life of doxycycline.

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

SPECIAL POPULATIONS

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

Tetracyclines are excreted into the breast milk in small amounts. Most exposed infants have very low blood levels of the drug and probably are not at risk [38]. 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 [179]. Limited studies indicate that short courses of the medication were not associated with dental side effects in this population [180].

The American Optometric Association asserts that tetracycline and its derivatives should not be given to children younger than 8 years of age or pregnant or nursing women.

(https://www.aoa.org/documents/optometrists/CPG-10.pdf. Last accessed January 22, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

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 [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. 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, with the exception of the formulation for the treatment of *C. difficile*-associated diarrhea/colitis [149]. 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 [157]. 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). 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. 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 [157]. 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 [158].

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 [149; 170].

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.

LIPOGLYCOPEPTIDES

In response to the increasing prevalence of multidrug resistance among clinical isolates of staphylococci and streptococci, glycopeptide analogues (lipoglycopeptides) with enhanced activity and favorable pharmacokinetics have been developed. In comparison to vancomycin, the lipoglycopeptides have greater potency against gram-positive bacteria, are active against vancomycin-resistant strains, and appear to be less likely to lead to emergence of resistant organisms [159; 160]. 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. In animal studies, lipoglycopeptides have proven effective in treating a variety of serious gram-positive infections, including bacteremia, pneumonia, and endocarditis [159; 160]. Clinical studies of efficacy in humans have been limited to date.

At present, three lipoglycopeptides, telavancin, dalbavancin, and oritavancin, have been approved by the FDA for the treatment of acute bacterial skin and soft-tissue infection. Clinical trials have shown equivalent or superior efficacy against MRSA skin infection compared with vancomycin [160; 161; 171]. The side effect profile is mild and comparable to other effective regimens. Reported adverse effects include headache, nausea, pruritus, pain at injection site, and fever.

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 [149].

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 [161; 162]. 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 [161].

PLEUROMUTILINS

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 [177]. Retapamulin was only approved for topical application, but in 2019 the first pleuromutilin—lefamulin—was approved for human use via oral and intravenous delivery. Pleuromutilin derivatives are designed primarily through modifications at the C(14) side chain [177].

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 [149]. The binding pocket of the bacterial ribosome closes around the mutilin core for an induced fit that prevents correct positioning of transfer RNA.

Retapamulin is used for the topical treatment of impetigo. A small amount is applied to the affected area twice per day for five days [149]. Possible side effects include eczema, application site reactions, diarrhea, headache, and nasopharyngitis.

Lefamulin is approved for the treatment of community-acquired bacterial pneumonia [178]. The usual dose is 600 mg every 12 hours for oral administration or 150 mg every 12 hours for IV use [149]. Treatment is generally at least five days; patients should be afebrile for ≥48 hours and clinically stable prior to discontinuation. The most common adverse reactions include diarrhea, nausea, injection site reactions, elevated liver enzymes, and vomiting [178]. It is contraindicated in patients with certain arrhythmias or who are prescribed drugs to prolong QT intervals.

INVESTIGATIONAL ANTIBIOTICS FOR DRUG-RESISTANT MICRO-ORGANISMS

Researchers continue to seek new methods and drugs to aid in the prevention of antibiotic resistance. Progress has been made in recent years, with two new antibiotics void of cross-resistance to 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 [172; 173]. 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 [172; 173]. 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 [172; 173].

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 [174; 175]. 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 [172; 173; 174; 175].

CONCLUSION

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 characteristics of each antimicrobial class, including important information such as indications, action, 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 that is specific 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.

Works Cited

1. Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. *CMAJ*. 2004;171(1):51-58.
2. Kaye KS, Fraimow HS, Abrutyn E. Pathogens resistant to antimicrobial agents: epidemiology, molecular mechanisms, and clinical management. *Infect Dis Clinics North Am*. 2000;14(2):293-319.
3. Neu HC. Overview of mechanisms of bacterial resistance. *Diagn Microbiol Infect Dis*. 1989;12(4 suppl):S109-S116.
4. Normark BH, Normark S. Evolution and spread of antibiotic resistance. *J Intern Med*. 2002;252(2):91-106.
5. Raymond DP, Kuehnert MJ, Sawyer RG. CDC/SIS position paper: preventing antimicrobial-resistant bacterial infections in surgical patients. *Surg Inf*. 2002;3(4):375-385.
6. Tomasz A. The mechanism of the irreversible antimicrobial effects of penicillins: how the beta-lactam antibiotics kill and lyse bacteria. *Annu Rev Microbiol*. 1979;33:113.
7. Livermore DM. Beta-lactamases in laboratory and clinical resistance. *Clin Microbiol Rev*. 1995;8(4):557-584.
8. Georgopapadakou NH. Penicillin-binding proteins and bacterial resistance to beta-lactams. *AntiMicrob Agents Chemother*. 1993;37(10):2045-2053.
9. Nathwani D, Wood MJ. Penicillins: a current review of their clinical pharmacology and therapeutic use. *Drugs*. 1993;45(6):866-894.
10. Bush LM, Johnson CC. Ureidopenicillins and beta-lactam/beta-lactamase inhibitor combinations. *Infect Dis Clin North Am*. 2000;14(2):409-433.
11. Richards ML, Prince RA, Kenaley KA, et al. Antimicrobial penetration into cerebrospinal fluid. *Drug Intell Clin Pharm*. 1981;15(5):341-368.
12. Tan JS, File TM Jr. Antipseudomonal penicillins. *Med Clin North Am*. 1995;79(4):679-693.
13. Watson ID, Boulton-Jones M, Stewart MJ, Henderson I, Payton CD. Pharmacokinetics of clavulanic acid-potentiated ticarcillin in renal failure. *Ther Drug Monit*. 1987;9(2):139-147.
14. Lin RY. A perspective on penicillin allergy. *Arch Intern Med*. 1992;152(5):930-937.
15. Babiak LM, Rybak MJ. Hematological effects associated with beta-lactam use. *Drug Intell Clin Pharm*. 1986;20(11):833-836.
16. Lacey CS. Interaction of dicloxacillin with warfarin. *Ann Pharmacother*. 2004;38(5):898.
17. Campbell BA, Cox SM. The penicillins. *Obstet Gynecol Clin North Am*. 1992;19(3):435-447.
18. Nau H. Clinical pharmacokinetics in pregnancy and perinatology. II. Penicillins. *Dev Pharmacol Ther*. 1987;10(3):174-198.
19. Kees F, Grobecker H. Systematics of beta-lactams: chemical properties and structure activity relationship of oral cephalosporins. *Antibiot Chemother*. 1995;47:1-7.
20. Fontana R, Cornaglia G, Ligozzi M, Mazzariol A. The final goal: penicillin-binding proteins and the target of cephalosporins. *Clin Microbiol Infect*. 2000;6(suppl 3):34-40.
21. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother*. 1990;26(suppl E):13-20.
22. Koch AL. Penicillin binding proteins, beta-lactams, and lactamases: offensives, attacks, and defensive countermeasures. *Crit Rev Microbiol*. 2000;26(4):205-220.
23. Hopkins JM, Towner KJ. Enhanced resistance to cefotaxime and imipenem associated with outer membrane protein alterations in *Enterobacter aerogenes*. *J Antimicrob Chemother*. 1990;25(1):49-55.
24. Gootz TD. Global dissemination of beta-lactamases mediating resistance to cephalosporins and carbapenems. *Expert Rev Anti Infect Ther*. 2004;2(2):317-327.
25. Neu HC. Pathophysiologic basis for the use of third-generation cephalosporins. *Am J Med*. 1990;88(suppl 4A):3S-11S.
26. Mazzei T, Dentico P. The pharmacokinetics of oral cephalosporins. *Clin Microbiol Infect*. 2000;6(suppl 3):53-54.
27. Borin MT. A review of the pharmacokinetics of cefpodoxime proxetil. *Drugs*. 1991;42(suppl 3):13-21.
28. Cherubin CE, Eng RH, Norrby R, et al. Penetration of newer cephalosporins into cerebrospinal fluid. *Rev Infect Dis*. 1989;11(4):526-548.
29. Balant LP, Dayer P, Fabre J. Consequences of renal insufficiency on the hepatic clearance of some drugs. *Int J Clin Pharmacol Res*. 1983;3(6):459-474.
30. Norrby SR. Side effects of cephalosporins. *Drugs*. 1987;34(suppl 2):105-120.
31. Tune BM. Renal tubular transport and nephrotoxicity of beta lactam antibiotics: structure-activity relationships. *Miner Electrolyte Metab*. 1994;20(4):221-231.
32. Famularo G, Polchi S, De Simone C. Acute cholecystitis and pancreatitis in a patient with biliary sludge associated with the use of ceftriazone: a rare but potentially severe complication. *Ann Ital Med Int*. 1999;14(3):202-204.
33. Alanis A, Weinstein AJ. Adverse reactions associated with the use of oral penicillins and cephalosporins. *Med Clin North Am*. 1983;67(1):113-129.

34. Seltsam A, Salama A. Ceftriaxone-induced immune haemolysis: two case reports and a concise review of the literature. *Intensive Care Med*. 2000;26(9):1390-1394.
35. Bechtold H, Andrassy K, Jahnchen E, et al. Evidence for impaired hepatic vitamin K1 metabolism in patients treated with *N*-methyl-thiotetrazole cephalosporins. *Thromb Haemost*. 1984;51:358-361.
36. McCue JD, Gal P, Pearson RC. Interference of new penicillins and cephalosporins with urine glucose monitoring tests. *Diabetes Care*. 1983;6(5):504-505.
37. Fulton B, Moore LL. Antiinfectives in breastmilk. Part I: penicillins and cephalosporins. *J Hum Lact*. 1992;8(3):157-158.
38. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776-789.
39. Kahan JS, Kahan FM, Goegleman R, et al. Thienamycin, a new beta-lactam antibiotic. I: discovery, taxonomy, isolation and physical properties. *J Antibiot*. 1979;32(1):1-12.
40. Rybak MJ. Resistance to antimicrobial agents: an update. *Pharmacotherapy*. 2004;24(12 pt 2):203S-215S.
41. Jones RN. Review of the in vitro spectrum of activity of imipenem. *Am J Med*. 1985;78(6A):22-32.
42. Drusano GL, Standiford HC. Pharmacokinetic profile of imipenem/cilastatin in normal volunteers. *Am J Med*. 1985;78(6A):47-53.
43. Andes DR, Craig WA. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. *Infect Dis Clin North Am*. 1999;13(3):595-618.
44. Leroy A, Fillastre JP, Borsa-Lebas F, et al. Pharmacokinetics of meropenem (ICI 194,660) and its metabolite (ICI 213,689) in healthy subjects and in patients with renal impairment. *Antimicrob Agents Chemother*. 1992;36(12):2794-2798.
45. Seto AH, Song JC, Guest SS. Ertapenem-associated seizures in a peritoneal dialysis patient. *Ann Pharmacother*. 2005;39(2):352-356.
46. Nacarkucuk E, Saglam H, Okan M. Meropenem decreases serum level of valproic acid. *Pediatr Neurol*. 2004;31(3):232-234.
47. Merrem IV [package insert]. Wilmington, DE: AstraZeneca; 2006.
48. Primaxin IM [package insert]. West Point, PA: Merck & Co.; 1985, 1998.
49. Odio CM, Puig JR, Feris JM, et al. Prospective, randomized, investigator-blinded study of the efficacy and safety of meropenem vs. cefotaxime in bacterial meningitis in children. Meropenem Meningitis Study Group. *Pediatr Infect Dis J*. 1999;18(7):581-590.
50. Ennis DM, Cobbs CG. The newer cephalosporins: aztreonam and imipenem. *Infect Dis Clin North Am*. 1995(3):687-713.
51. Duma RJ, Berry AJ, Smith SM, et al. Penetration of aztreonam into cerebrospinal fluid of patients with and without inflamed meninges. *Antimicrob Agents Chemother*. 1984;26(5):730-733.
52. Sattler FR, Schramm M, Swabb EA. Safety of aztreonam and SQ 26992 in elderly patients with renal insufficiency. *Rev Infect Dis*. 1985;7(suppl 4):S622-S627.
53. Fillastre JP, Leroy A, Baudoin C, et al. Pharmacokinetics of aztreonam in patients with chronic renal failure. *Clin Pharmacokinet*. 1985;10(1):91-100.
54. Alvan G, Nord CE. Adverse effects of monobactams and carbapenems. *Drug Saf*. 1995;12(5);305-313.
55. Perez Pimiento A, Gomez Martinez M, Minguez Mena A, Trampal Gonzalez A, De Paz Arranz S, Rodriguez Mosquera M. Aztreonam and ceftazidime: evidence of in vivo cross-allergenicity. *Allergy*. 1998;53(6):624-625.
56. Azactam [package insert]. Princeton, NJ: Bristol-Myers Squibb Co.; 2007.
57. Azactam [package insert]. Princeton, NJ: Bristol-Myers Squibb Co.; 2004.
58. Bosso JA, Black PG. Controlled trial of aztreonam vs. tobramycin and azlocillin for acute pulmonary exacerbations of cystic fibrosis. *Pediatr Infect Dis J*. 1988;7(3):171-176.
59. Moellering RC Jr. In vitro antibacterial activity of the aminoglycoside antibiotics. *Rev Infect Dis*. 1983;5(Suppl):S212-S232.
60. Kotra LP, Haddad J, Mobashery S. Aminoglycosides: perspectives on mechanisms of action and resistance and strategies to counter resistance. *Antimicrob Agents Chemother*. 2000;44(12):3249-3256.
61. Gordon S, Swenson JM, Hill BC, et al. Antimicrobial susceptibility patterns of common and unusual species of enterococci causing infections in the United States. Enterococcal Study Group. *J Clin Microbiol*. 1992;30(9):2373-2378.
62. Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med*. 1993;328(24):1740-1746.
63. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin North Am*. 2003;17(3):503-528.
64. Appel GB. Aminoglycoside nephrotoxicity. *Am J Med*. 1990;88(suppl 3C):S16-S20; discussion 38S-42S.
65. Lietman PS. Liver disease, aminoglycoside antibiotics and renal dysfunction. *Hepatology*. 1988;8(4):966-968.
66. Pandya A, Xia X, Radnaabazar J, et al. Mutation in the mitochondrial 12S rRNA gene in two families from Mongolia with matrilineal aminoglycoside ototoxicity. *J Med Genet*. 1997;34(2):169-172.
67. Hokkanen E. The aggravating effect of some antibiotics on the neuromuscular blockade in myasthenia gravis. *Acta Neurol Scand*. 1964;40:346-352.
68. Streptomycin Sulfate [package insert]. New York, NY: Pfizer Inc.; 1998.

69. Alkadi HO, Nooman MA, Raja'a YA. Effect of gentamicin on serum digoxin level in patients with congestive heart failure. *Pharm World Sci*. 2004;26(2):107-109.
70. Tobramycin Solution for Inhalation [package insert]. Seattle, WA: Pathogenesis Corp.; 1998.
71. Dashe JS, Gilstrap LC III. Antibiotic use in pregnancy. *Obstet Gynecol Clin North Am*. 1997;24(3):617-629.
72. Goldman RC, Fesik SW, Doran CC. Role of protonated and neutral forms of macrolides in binding to ribosomes from gram-positive and gram-negative bacteria. *Antimicrob Agents Chemother*. 1990;34(3):426-431.
73. File TM. Telithromycin new product overview. *J Allergy Clin Immunol*. 2005;115(2):S1-S13.
74. Sun H, Maglio D, Nicolau D. Macrolide resistance in *Streptococcus pneumoniae*: mechanisms, patterns, and clinical implications of resistance. *Conn Med*. 2004;68(9):571-576.
75. Matsuoka M, Sasaki T. Inactivation of macrolides by producers and pathogens. *Curr Drug Targets Infect Disord*. 2004;4(3):217-240.
76. Doern GV, Jorgensen JH, Thornsberry C, et al. National collaborative study of the prevalence of antimicrobial resistance among clinical isolates of *Haemophilus influenzae*. *Antimicrob Agents Chemother*. 1988;32(2):180-185.
77. Malmborg AS. Effect of food on absorption of erythromycin: a study of two derivatives, the stearate and the base. *J Amtimicrob Chemother*. 1979;5(5):591-599.
78. Bahal N, Nahata MC. The new macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. *Ann Pharmacother*. 1992;26(1):46-55.
79. Periti P, Mazzei T, Mini E, Novelli A. Clinical pharmacokinetic properties of the macrolide antibiotics: effects of age and various pathophysiological states (Part II). *Clin Pharmacokinet*. 1989;16(5):261-282.
80. Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am*. 2004;18(3): 621-649.
81. Clark JP, Langston E. Ketolides: a new class of antibacterial agents for treatment of community-acquired respiratory tract infections in a primary care setting. *Mayo Clin Proc*. 2003;78(9):1113-1124.
82. Katapadik K, Kostandy G, Katapadi M, et al. A review of erythromycin-induced malignant tachyarrhythmia—torsade de pointes: a case report. *Angiology*. 1997;48:821-826.
83. Guay DR, Patterson DR, Seipman N, Craft JC. Overview of the tolerability profile of clarithromycin in preclinical and clinical trials. *Drug Saf*. 1993;8(5):350-364.
84. Wellington K, Noble S. Telithromycin. *Drugs*. 2004;64(15):1683-1694.
85. Ludden TM. Pharmacokinetic interactions of the macrolide antibiotics. *Clin Pharmacokinet*. 1985;10:63-79.
86. Kahri AJ, Valkonen MM, Vuoristo MK, Pentikainen PJ. Rhabdomyolysis associated with concomitant use of simvastatin and clarithromycin. *Ann Pharmacother*. 2004;38(4):719.
87. Desta Z, Soukhova N, Flockhart DA. In vitro inhibition of pimozide *N*-dealkylation by selective serotonin reuptake inhibitors and azithromycin. *J Clin Psychopharmacol*. 2002;22(2):162-168.
88. Watkins VS, Polk RE, Stotka JL. Drug interactions of macrolides: emphasis on dirithromycin. *Ann Pharmacother*. 1997;31(3): 349-356.
89. Kolilekas L, Anagnostopoulos GK, Lampaditis I, Eleftheriadis I. Potential interaction between telithromycin and warfarin. *Ann Pharmacother*. 2004;38(9):1424-1427.
90. Centers for Disease Control and Prevention. *Chlamydia trachomatis* infections: policy guidelines for prevention and control. *MMWR*. 1985;34(3-S):S53-S74.
91. Kacmar J, Cheh E, Montagno A, Peipert JF. A randomized trial of azithromycin versus amoxicillin for the treatment of *Chlamydia trachomatis* in pregnancy. *Infect Dis Obstet Gynecol*. 2001;9(4):197-202.
92. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiol Drug Saf*. 2000;9(7):549-556.
93. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol*. 1998;15(9):523-525.
94. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Saf*. 2002;25(13):929-942.
95. Andersson MI, MacGowan AP. Development of the quinolones. *J Antimicrob Chemother*. 2003;51(Suppl 1):1-11.
96. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiol Mol. Biol R*. 1997;61(3):377-392.
97. Willmott CJ, Maxwell A. A single point mutation in the DNA gyrase A protein greatly reduces binding of fluoroquinolones to the gyrase-DNA complex. *Antimicrob Agents Chemother*. 1993;37:126-127.
98. Mammeri H, Van De Loo M, Poirel L, Martinez-Martinez l, Nordmann P. Emergence of plasmid-mediated quinolone resistance in *Escherichia coli* in Europe. *Antimicrob Agents Chemother*. 2005;49(1):71-76.
99. Blondeau JM. A review of the comparative in-vitro activities of 12 antimicrobial agents, with a focus on five new respiratory quinolones. *J Antimicrob Chemother*. 1999;43(suppl B):1-11.

100. Sorgel F, Kinzig M. Pharmacokinetics of gyrase inhibitors, part 1: basic chemistry and gastrointestinal disposition. *Am J Med.* 1993;94(3A):S44-S55.
101. Sorgel F, Kinzig M. Pharmacokinetics of gyrase inhibitors, part 2: renal and hepatic elimination pathways and drug interactions. *Am J Med.* 1993; 94(3A):S56-S69.
102. Moise PA, Birmingham MC, Schentag JJ. Pharmacokinetics and metabolism of moxifloxacin. *Drugs Today*. 2000;36(4):229-244.
103. Fillastre JP, Leroy A, Moulin B, Dhib M, Borsa-Lebas F, Humbert G. Pharmacokinetics of quinolones in renal insufficiency. *J Antimicrob Chemother*. 1990;26(suppl B):51-60.
104. Cohen JS. Peripheral neuropathy associated with fluoroquinolones. *Ann Pharmacother*. 2001;35(12):1540-1547.
105. Zabraniecki L, Negrier I, Vergne P, et al. Fluoroquinolone induced tendinopathy: report of 6 cases. *J Rheumatol.* 1996;23(3): 516-520.
106. Oh YR, Carr-Lopez SM, Probasco JM, Crawley PG. Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother*. 2003;37(7-8):1010-1013.
107. Coleman CI, Spencer JV, Chung JO, Reddy P. Possible gatifloxacin-induced fulminant hepatic failure. *Ann Pharmacother*. 2002;36(7-8):1162-1167.
108. Lin G, Hays DP, Spillane L. Refractory hypoglycemia from ciprofloxacin and glyburide interaction. *J Toxicol Clin Toxicol.* 2004;42(3):295-297.
109. Polk RE, Healy DP, Sahai J, Drwal L, Racht E. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. *Antimicrob Agents Chemother*. 1989;33(11):1841-1844.
110. Hori S, Kizu J, Kawamura M. Effects of anti-inflammatory drugs on convulsant activity of quinolones: a comparative study of drug interaction between quinolones and anti-inflammatory drugs. *J Infect Chemother*. 2003;9(4):314-320.
111. Radandt JM, Marchbanks CR, Dudley MN. Interactions of fluoroquinolones with other drugs: mechanisms, variability, clinical significance, and management. *Clin Infect Dis*. 1992;14(1):272-284.
112. Von Keutz E, Ruhl-Fehlert C, Drommer W, Rosenbruch M. Effects of ciprofloxacin on joint cartilage in immature dogs immediately after dosing and after a 5-month treatment-free period. *Arch Toxicol.* 2004;78(7):418-424.
113. Grady R. Safety profile of quinolone antibiotics in the pediatric population. *Pediatr Infect Dis J*. 2003;22(12):1128-1132.
114. Redmond A, Sweeney L, MacFarland M, Mitchell M, Daggett S, Kubin R. Oral ciprofloxacin in the treatment of *Pseudomonas* exacerbations of paediatric cystic fibrosis: clinical efficacy and safety evaluation using magnetic resonance image scanning. *J Int Med Res*. 1998;26(6):304-312.
115. Woods DD. Relation of p-aminobenzoic acid to mechanism of action of sulphanilamide. *Br J Exp Pathol.* 1940;21:74-90.
116. Radstrom P, Fermer C, Kristiansen BE, Jenkins A, Skold O, Swedberg G. Transformational exchanges in the dihydropteroate synthetase gene of *Neisseria meningitidis*: a novel mechanism for acquisition of sulfonamide resistance. *J Bacteriol.* 1992;174(20):6386-6393.
117. Then RL. Mechanisms of resistance to trimethoprim, the sulfonamides and trimethoprim-sulfamethoxazole. *Rev Infect Dis*. 1982;4(2):261-269.
118. Bushby SRM. Trimethoprim-sulfamethoxazole: in vitro microbiologic aspects. *J Infect Dis*. 1973;128(suppl):442-462.
119. Houvinen P. Trimethoprim resistance. *Antimicrob Agents Chemother*. 1987;31(10):1451-1456.
120. Hekster CA, Vree TB. Clinical pharmacokinetics of sulphonamides and their N4-acetyl derivatives. *Antibiot Chemother*. 1982;31:118-122.
121. Foltzer MA, Reese RE. Trimethoprim-sulfamethoxazole and other sulfonamides. *Med Clin North Am*. 1987;71(6):1177-1194.
122. Lawson DH, Paice BJ. Adverse reactions to trimethoprim-sulfamethoxazole. *Rev Infect Dis*. 1982;4(2):429-433.
123. Keisu M, Wiholm BE, Palmblad J. Trimethoprim-sulphamethoxazole-associated blood dyscrasias: ten years' experience of the Swedish spontaneous reporting system. *J Intern Med*. 1990;228(4):353-360.
124. Markowitz N, Saravolatz LD. Use of trimethoprim-sulfamethoxazole in a glucose-6-phosphate dehydrogenase-deficient population. *Rev Infect Dis*. 1987;9:S218-S229.
125. Kaufman JM, Fauver HE Jr. Potentiation of warfarin by trimethoprim-sulfamethoxazole. *Urology*. 1980;16(6):601-603.
126. Campana C, Regazzi MB, Buggia I, Molinaro M. Clinically significant drug interactions with cyclosporine: an update. *Clin Pharmacokinet*. 1996;30(2):141-179.
127. Springer C, Eyal F, Michael J. Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. *J Pediatr*. 1982;100(4):647-650.
128. Silvadene Cream [package insert]. Bristol, TN: King Pharmaceuticals; 2003.
129. Craven GR, Gavin R, Fanning T. The transfer RNA binding site of the 30 S ribosome and the site of tetracycline inhibition. *Cold Spring Symp Quant Biol.* 1969;34:129-137.
130. Schnappinger D, Hillen W. Tetracyclines: antibiotic action, uptake, and resistance mechanisms. *Arch Microbiol.* 1996;165(6): 359-369.

131. Speer BS, Shoemaker NB, Salyers AA. Bacterial resistance to tetracycline: mechanisms, transfer, and clinical significance. *Clin Microbiol Rev*. 1992;5(4):387-399.

132. Forrest JN, Cox M, Hong C, Morrison G, Bia M, Singer I. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med*. 1978;298(4):173-177.

133. Karlsson M, Hammers S, Nilsson-Ehle I, Malmborg AS, Wretlind B. Concentrations of doxycycline and penicillin G in sera and cerebrospinal fluid of patients treated for neuroborreliosis. *Antimicrob Agents Chemother*. 1996;40(5):1104-1107.

134. Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother*. 1985;28(2):347-348.

135. Forti G, Benincori C. Doxycycline and the teeth. *Lancet*. 1969;1(7598):782.

136. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet*. 1988;15(6):355-366.

137. Houin G, Brunner F, Nebout T, Chereaoui M, Lagrue G, Tillement JP. The effects of chronic renal insufficiency on the pharmacokinetics of doxycycline in man. *Br J Clin Pharmacol*. 1983;16(3):245-252.

138. Vial T, Biour M, Descotes J, Trepo C. Antibiotic-associated hepatitis: update from 1990. *Ann Pharmacother*. 1997;31(2):204-220.

139. Angeloni VL, Salasche SJ, Ortiz R. Nail, skin, and scleral pigmentation induced by minocycline. *Cutis*. 1987;40(3):229-233.

140. Byrne PA, Williams BD, Pritchard MH. Minocycline-related lupus. *Br J Rheumatol*. 1994;33:674-676.

141. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet*. 1990;18(3): 210-219.

142. Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. *Br Med J*. 1980;280(6210):293.

143. Dickinson BD, Altman RD, Nielsen NH, Sterling ML, Council on Scientific Affairs, American Medical Association. Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol*. 2001;98(5 pt 1):853-860.

144. Danos EA. Apparent potentiation of warfarin activity by tetracycline. *Clin Pharm*. 1992;11(9):806-808.

145. Rodin SM, Johnson BF. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet*. 1988;15(4):227-244.

146. Frost HM. Tetracyclines and fetal bones. *Henry Ford Hosp Med J*. 1965;13(4):403-410.

147. Allen ES, Brown WE. Hepatic toxicity of tetracycline in pregnancy. *Am J Obstet Gynecol*. 1966;95(1):12-18.

148. *Mosby's Drug Consult 2007*. 17th edition. St. Louis, MO; Mosby, Inc; 2006.

149. Lexicomp Online. Available at http://online.lexi.com. Last accessed January 11, 2018.

150. Allchin D. Penicillin and Chance. Available at http://shipseducation.net/sacredbovines/SB-Penicillin-chance.htm. Last accessed January 3, 2018.

151. Hwa-Froelich DA, Westby CE. Considerations when working with interpreters. *Communication Disorders Quarterly*. 2003;4(2): 78-85.

152. Saravolatz LD, Stein GE, Johnson LB. Ceftaroline: a novel cephalosporin with activity against methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2011;52(9):1156-1163.

153. File TM Jr, Wilkoz MH, Stein GE. Summary of ceftaroline fosamil clinical trial studies and clinical safety. *Clin Infect Dis*. 2012;55(suppl 3): S173-S180.

154. Low DE, File TM Jr, Eckburg PB, et al. FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. *J Antimicrob Chemother*. 2011;66(Suppl 3):iii33-iii44.

155. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA Requires Label Changes to Warn of Risk for Possibly Permanent Nerve Damage from Antibacterial Fluoroquinolone Drugs Taken by Mouth or by Injection. Available at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM365078.pdf. Last accessed January 10, 2018.

156. Reynolds PE. Structure, biochemistry and mechanism of action of glycopeptide antibiotics. *Eur J Clin Microbiol Infect Dis*. 1989;8(11):943-950.

157. Rybak MJ, Lomaestro BM, Rotachafer JC, et al. Therapeutic monitoring of vancomycin in adults: summary of consensus recommendations for the American Society of Health-System Pharmacists, the Infectious Disease Society of America, and the Society of Infectious Disease Pharmacists. *Pharmacotherapy*. 2009;29:1275-1279.

158. Mergenhagen KA, Borton AR. Vancomycin nephrotoxicity: a review. *J Pharm Pract*. 2014;27(6):545-553.

159. Guskey MT, Tsuji BT. A comparative review of the lipoglycopeptides: oritavancin, dalbavancin, and telavancin. *Pharmacotherapy*. 2010;30:80-94.

160. Zhanel GG, Calic D, Schweizer F, et al. New lipoglycopeptides: a comparative review of dalbavancin, oritavancin and telavancin. *Drugs*. 2010;70(7):859-886.

161. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. *N Engl J Med*. 2014;370(23):2169-2179.

162. Bradley JS, Puttagunta S, Rubino CM, Blumer JL, Dunne M, Sullivan JE. Pharmacokinetics, safety, and tolerability of single dose dalbavancin in children 12 through 17 years of age. *Pediatr Infect Dis J*. 2015;34(7):748-752.

163. U.S. Food and Drug Administration. FDA Approves New Antibacterial Drug. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573955.htm. Last accessed January 9, 2018.

164. Centers for Disease Control and Prevention. Antibiotic/Antimicrobial Resistance. Available at https://www.cdc.gov/drugresistance/index.html. Last accessed January 3, 2018.

165. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med*. 2001;161(1):15–21.

166. Herbert ME, Brewster GS, Lanctot-Herbert M. Ten percent of patients who are allergic to penicillin will have serious reactions if exposed to cephalosporins. *Western Journal of Medicine*. 2000;172(5):341.

167. Bhattacharya S. The facts about penicillin allergy: a review. *J Adv Pharm Technol Res*. 2010;1(1):11-17.

168. American College of Allergy, Asthma, and Immunology. Penicillin Allergy: Facts for Patients. Available at http://college.acaai.org/sites/default/files/Patient%20factsheet.%20Penicillin%20allergy.%20Facts%20for%20patients.pdf. Last accessed January 4, 2018.

169. Spasovski G, Vanholder R, Allolio B, et al. Hyponatraemia guideline development group: clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*. 2014;170(3):G1-G47.

170. United States Food and Drug Administration. Intraocular Injections of a Compounded Triamcinolone, Moxifloxacin, and Vancomycin (TMV) Formulation: FDA Statement - Case of Hemorrhagic Occlusive Retinal Vasculitis. Available at https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm578743.htm. Last accessed January 9, 2018.

171. Crotty MP, Krekel T, Burnham C-AD, Ritchie DJ. New Gram-positive agents: the next generation of oxazolidinones and lipoglycopeptides. *J Clin Microbiol*. 2016;54:2225-2232.

172. Parmar A, Iyer A, Vincent CS, et al. Efficient total syntheses and biological activities of two teixobactin analogues. *Chem Commun*. 2016;52:6060-6063.

173. Ling LL, Schneider T, Peoples AJ, et al. A new antibiotic kills pathogens without detectable resistance. *Nature*. 2015;517:455-459.

174. Maffioli SI, Zhang Y, Degen D, et al. Antibacterial nucleoside-analog inhibitor of bacterial RNA polymerase. 2017;169(7):1240-1248.

175. American Association for the Advancement of Science. Researchers Discover New Antibiotic Effective Against Drug-Resistant Bacteria. Available at https://www.eurekalert.org/pub_releases/2017-06/ru-rdn060817.php. Last accessed January 10, 2018.

176. U.S. Food and Drug Administration. FDA Updates Warnings for Fluoroquinolone Antibiotics on Risks of Mental Health and Low Blood Sugar Adverse Reactions. Available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm612995.htm. Last accessed July 12, 2018.

177. Novak R, Shlaes DM. The pleuromutilin antibiotics: a new class for human use. *Curr Opin Investig Drugs*. 2010;11(2):182-191.

178. U.S. Food and Drug Administration. FDA Approves New Antibiotic to Treat Community-Acquired Bacterial Pneumonia. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia. Last accessed November 1, 2019.

179. Centers for Disease Control and Prevention. Rocky Mountain Spotted Fever: Treatment. Available at https://www.cdc.gov/rmsf/healthcare-providers/treatment.html. Last accessed May 14, 2020.

180. Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. *J Pediatr*. 2015;166(5):1246-1251.

Evidence-Based Practice Recommendations Citations

Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-455. Available at https://www.cdc.gov/HAI/pdfs/cdiff/Cohen-IDSA-SHEA-CDI-guidelines-2010.pdf. Last accessed January 22, 2018.

Davey P, Marwick CA, Scott CL, et al. Improving how physicians working in hospital settings prescribe antibiotics. *Cochrane Database System Rev*. 2017;(4):CD003543. Available at http://www.cochrane.org/CD003543/EPOC_improving-how-physicians-working-hospital-settings-prescribe-antibiotics. Last accessed January 22, 2018.

American Optometric Association. *Care of the Patient with Ocular Surface Disorders*. St. Louis, MO: American Optometric Association; 2010. Available at https://www.aoa.org/documents/optometrists/CPG-10.pdf. Last accessed January 22, 2018.