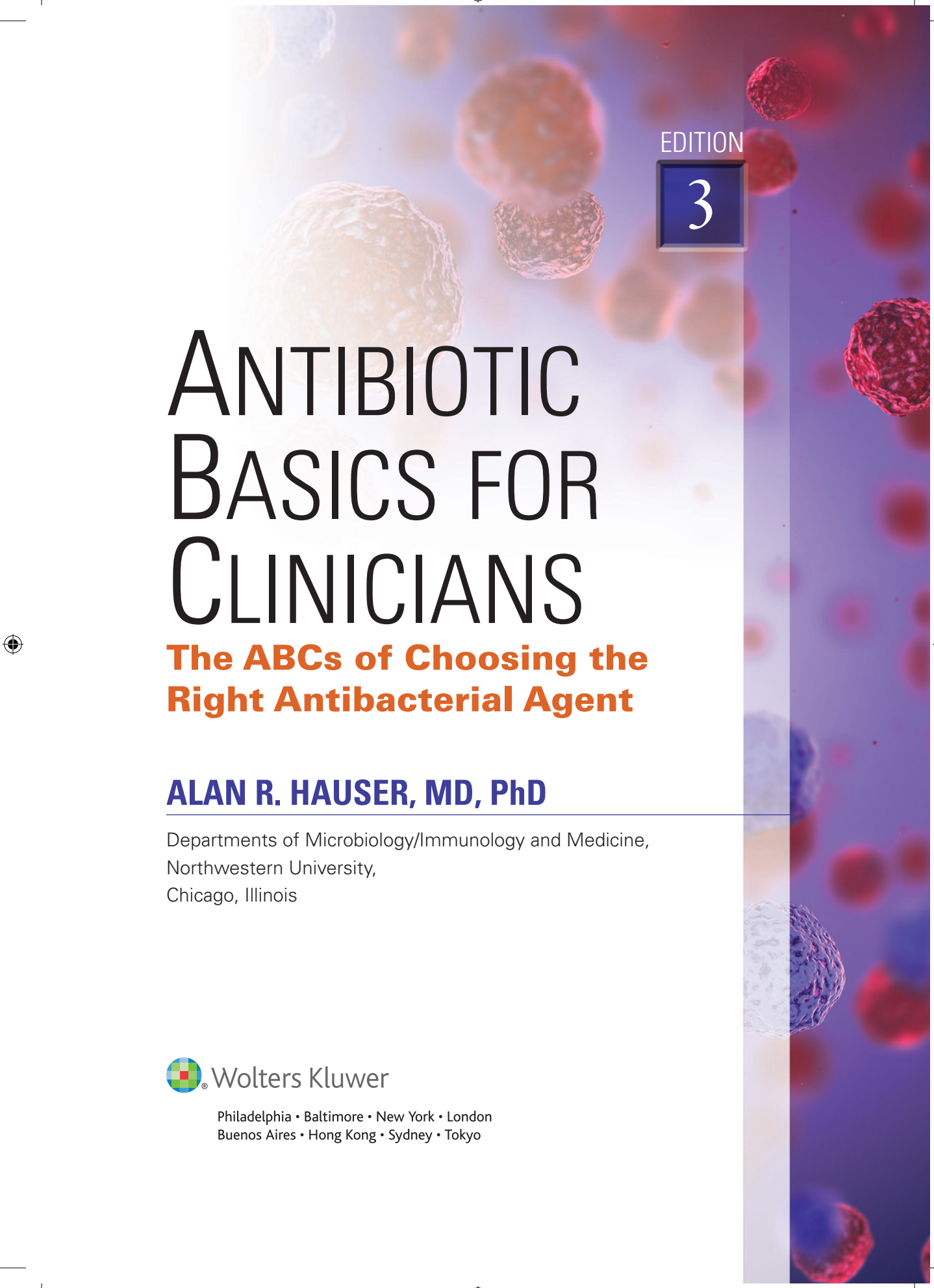

EDITION

3

ANTIBIOTIC BASICS FOR CLINICIANS

The ABCs of Choosing the Right Antibacterial Agent

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Third Edition

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Dedicated to Anne, Grace, and John

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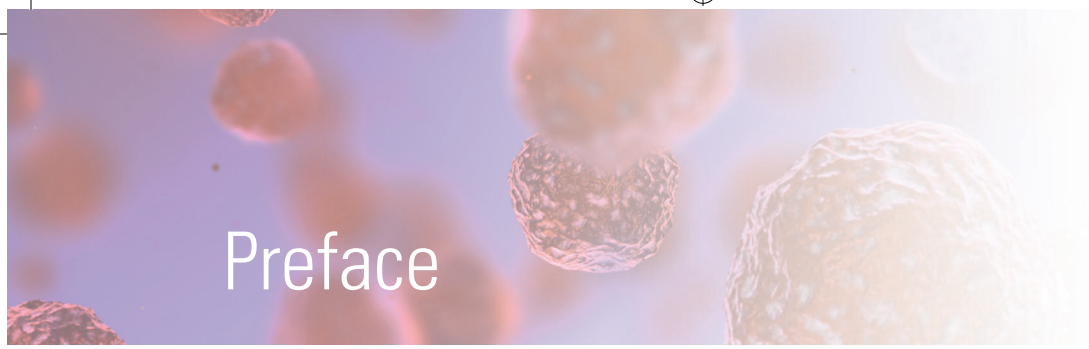

Preface

Which is more difficult: learning a large body of information or applying the newly learned information? Although the answer is debatable, it is clear that health care professionals must do both. Most health care training programs consist of an initial phase of classroom lectures and small group sessions in which the intricacies of cranial nerves, the Krebs cycle, and renal physiology are mastered. Following this phase, trainees suddenly are immersed in the real world of patients who present with complaints of a cough, a painful lower back, or a fever. As an infectious disease subspecialist, I have often seen this culture shock expressed as the blank look of a medical student when asked, "So, what antibiotic should we start this patient on?" Obviously, a basic understanding of the principles of pharmacology and microbiology is insufficient for most trainees when suddenly faced with the complexities of an infected patient.

This book is not only meant to be a guide to antibiotics for students studying to be physicians, nurses, physician assistants, pharmacologists, or medical technologists but should also proves useful for residents, fellows, and practicing clinicians. It is designed to serve as a bridge between the book knowledge acquired during the initial phases of training and the reflexive prescribing habits of experienced practitioners. Just as the initial bewildering complexities of electrocardiograms and chest radiographs disappear when the first principles underlying these tests are appreciated and understood, so too do the difficulties of antibiotic selection. This book provides the rationale behind antibiotic selection for many common bacterial pathogens and infectious disease presentations so that much of the memorization (and magic and mystery) that usually accompanies proper prescribing of antibiotics is eliminated. Where memorization is unavoidable, learning aids are presented that make the process as painless as possible.

This book can be easily read and comprehended in one or two weeks by a busy student or practitioner. As a result, it is not a comprehensive guide to the antibiotic metropolis but merely an outline of the major thoroughfares of antibiotic therapy so that readers can more easily fill in the residential streets and alleys as they gain experience. In terms of the war analogy used throughout the book, the emphasis is on strategy, not tactics. Thus, only commonly used antibiotics are mentioned, and some oversimplification and omissions are unavoidable. It is hoped that the reader will be able to master the major concepts and rules so that with subsequent clinical exposure and practice, the nuances and exceptions to these rules may be assimilated.

The scope of this volume is limited to antibacterial agents, arguably the most complex and frequently encountered antibiotics that must be mastered by health care practitioners. Future volumes will address antiviral, antifungal, and antiparasitic agents.

The third edition of this book has been updated and expanded to include newer antibiotics that have become available during the past five years. Likewise, sections have been updated to reflect recent changes in treatment guidelines, such as those pertaining to pneumonia and *Neisseria gonorrhoeae*. Where necessary, updated references have been added.

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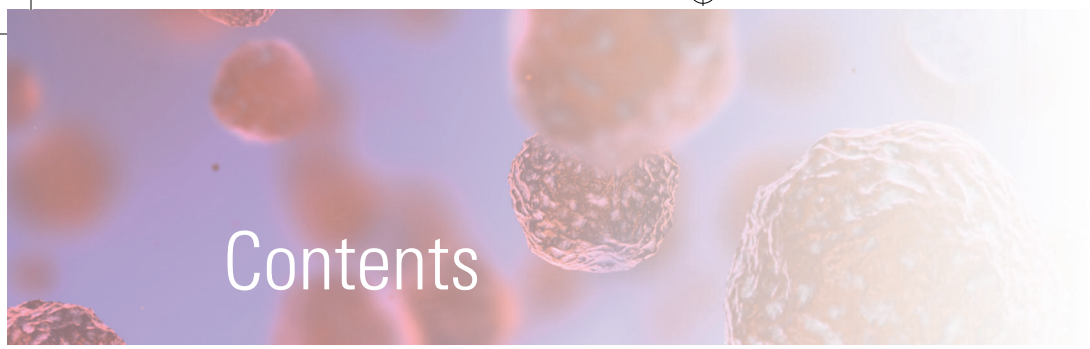
After completing this book, it is hoped that the reader will view antibiotics as valuable friends in the fight against infectious diseases and not as incomprehensible foes blocking his or her progress toward clinical competency. In addition, the reader will obtain a foundation that can be built upon throughout his or her career, as new antibiotics become available.

I am indebted to many people who have contributed in large and small ways to this book but would especially like to acknowledge a few individuals. Many thanks to Mike Postelnick, Kristin Darin, and Marc Scheetz for advice and for reviewing portions of this book; Andy Rabin for providing quotes from the medieval literature; and Joe Welch for invaluable advice. Thank you to Kathleen Scogna, Michael Brown, and Steve Boehm at Lippincott Williams & Wilkins for their assistance, patience, and advice in bringing this project to fruition, and to Jeremiah Kiely and Amy Millholen for help throughout the process of putting together the third edition of this book. I am grateful to the intelligent and inquisitive medical students at Northwestern University who asked the many questions that inspired this book. And finally, I wish to thank my wife, Anne, and my children, Grace and John, who kept me smiling throughout the whole process.



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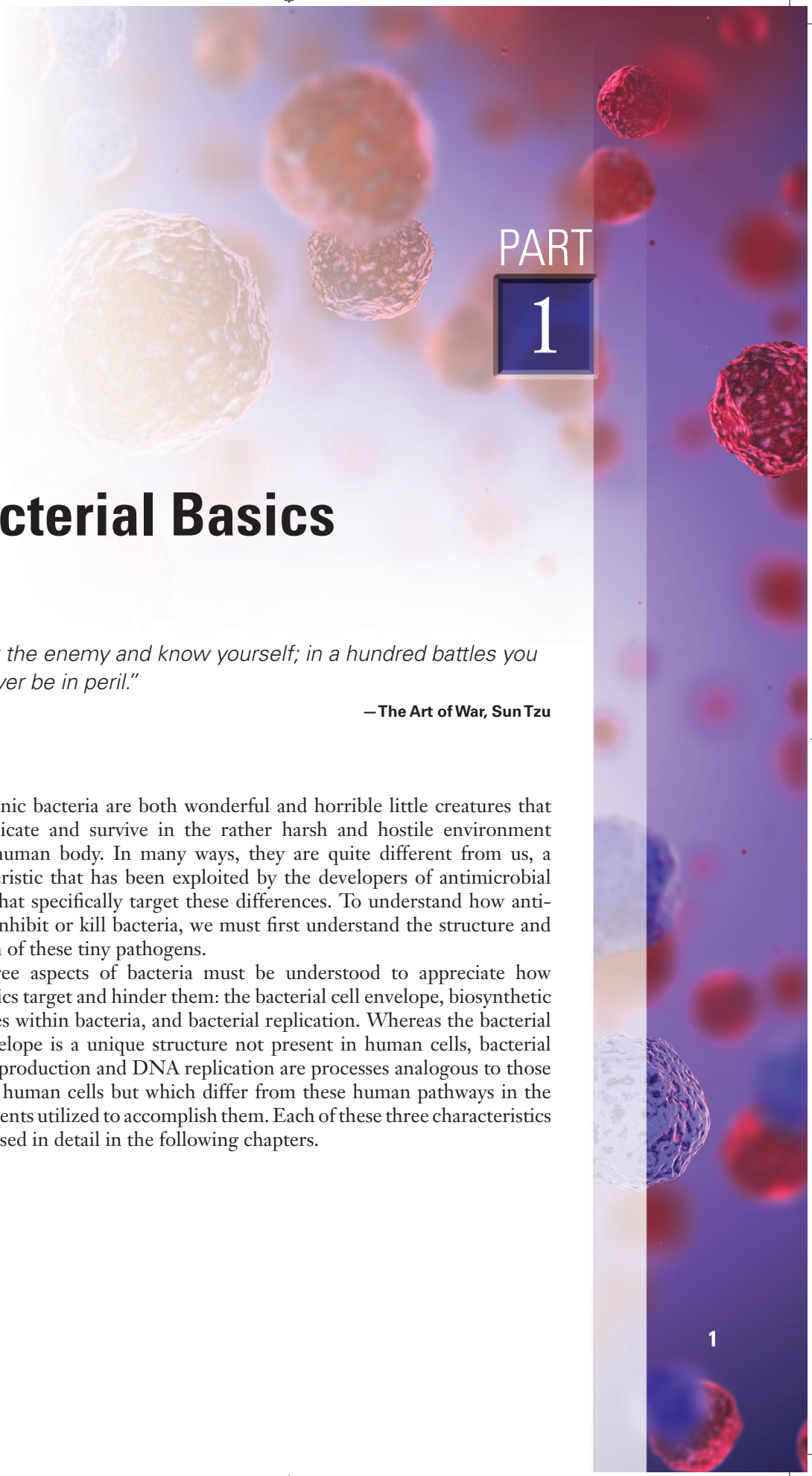

PART 1

Bacterial Basics

"Know the enemy and know yourself; in a hundred battles you will never be in peril."

—The Art of War, Sun Tzu

Pathogenic bacteria are both wonderful and horrible little creatures that self-replicate and survive in the rather harsh and hostile environment of the human body. In many ways, they are quite different from us, a characteristic that has been exploited by the developers of antimicrobial agents that specifically target these differences. To understand how antibiotics inhibit or kill bacteria, we must first understand the structure and function of these tiny pathogens.

Three aspects of bacteria must be understood to appreciate how antibiotics target and hinder them: the bacterial cell envelope, biosynthetic processes within bacteria, and bacterial replication. Whereas the bacterial cell envelope is a unique structure not present in human cells, bacterial protein production and DNA replication are processes analogous to those used by human cells but which differ from these human pathways in the components utilized to accomplish them. Each of these three characteristics is discussed in detail in the following chapters.

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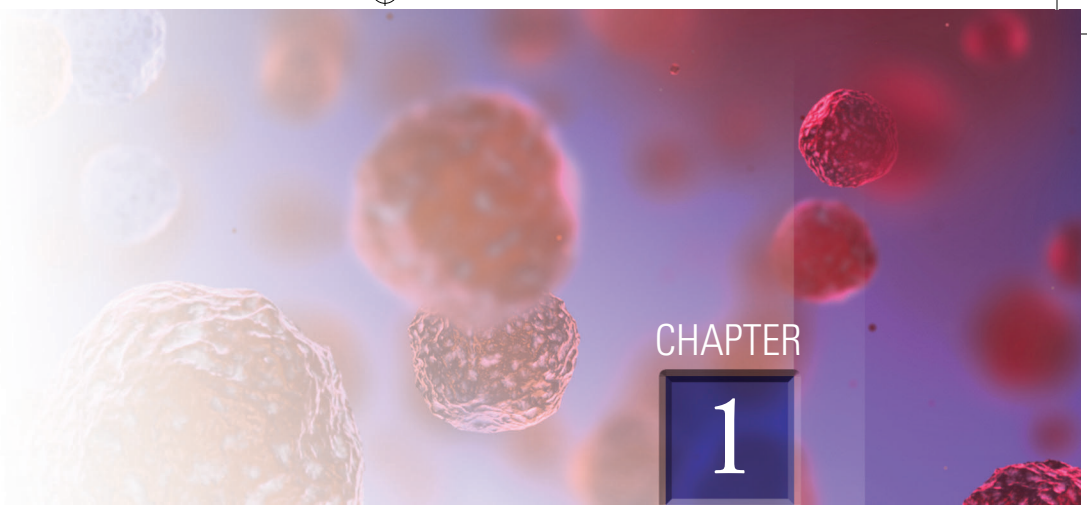

CHAPTER 1

Cell Envelope

"While styles of armor varied and changed from one decade to the next, the basics were a suit of plate armor consisting of a chest piece, a skirt of linked hoops, and arm and leg pieces, all worn over a hauberk or shirt of chain mail and a leather or padded tunic, or a tight-fitting surcoat. . . . Chain mail covered the neck, elbows, and other joints; gauntlets of linked plates protected the hands."

—A Distant Mirror, Barbara W. Tuchman

The **cell envelope** is a protective layer of armor that surrounds the bacterium and allows it to survive in diverse and extreme environments. The cell envelopes of some bacteria consist of a **cytoplasmic membrane** surrounded by a tough and rigid mesh called a cell wall (Fig. 1-1); these bacteria are referred to as **gram-positive** bacteria. In contrast, the cell envelope of a **gram-negative** bacterium consists of a cytoplasmic membrane surrounded by a thin cell wall that is itself surrounded by a second lipid membrane called the **outer membrane**. The outer membrane contains large amounts of **lipopolysaccharide (LPS)**, a molecule that is very toxic to humans. The space between the outer membrane and the cytoplasmic membrane, which contains the cell wall, is called the **periplasmic space** or the **periplasm**. Whether a bacterium is gram-positive or gram-negative can usually be determined by a technique called Gram staining, which colors gram-positive bacteria blue or purple and gram-negative bacteria pink. Gram staining is often the first step used by a hospital microbiology laboratory in identifying an unknown bacterium from a clinical specimen.

As in human cells, the cytoplasmic membrane prevents ions from flowing into or out of the cell itself and maintains the cytoplasm and bacterial components in a defined space. The cell wall is a tough layer that gives a bacterium its characteristic shape and protects it from mechanical and osmotic stresses. In gram-negative bacteria, the

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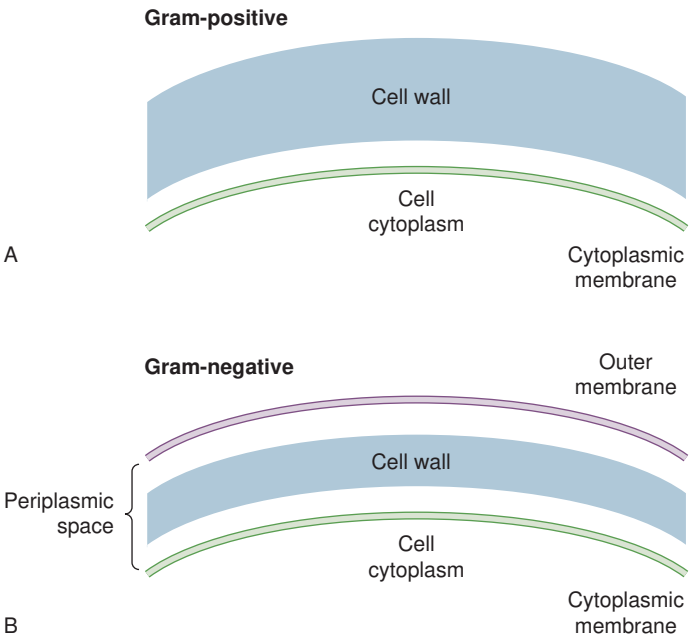

Figure 1-1. Structure of the bacterial cell envelope. **A.** Gram-positive. **B.** Gram-negative.

outer membrane acts as an additional protective barrier and prevents many substances from penetrating into the bacterium. This layer, however, does contain channels called **porins** that allow some compounds such as molecules used in metabolism by the bacterium to pass through.

Because human cells do not possess a cell wall, this structure is an ideal target for antimicrobial agents. To appreciate how these agents work, we must first understand the structure of the cell wall. This complex assembly is made up of a substance called **peptidoglycan**, which itself consists of long sugar polymers. The polymers are repeats of two sugars: *N*-acetylglucosamine and *N*-acetylmuramic acid (Fig. 1-2). If the cell wall were to consist of these polymers alone, it would be quite weak. However, peptide side chains extend from the sugars in the polymers and form cross-links, one peptide to another. These cross-links greatly strengthen the cell wall, just as cross-linking of metal loops strengthened the chain mail armor used by medieval knights.

The cross-linking of peptidoglycan is mediated by bacterial enzymes called **penicillin-binding proteins (PBPs)**. (The reason for this nomenclature becomes apparent in later chapters.) These enzymes recognize the terminal two amino acids of the peptide side chains, which are usually D-alanine–D-alanine, and either directly cross-link them to a second peptide side chain or indirectly cross-link them by forming a bridge of glycine residues between the two peptide side chains.

The formation of a tough cross-linked cell wall allows bacteria to maintain a characteristic shape. For example, some bacteria are rod shaped and referred to as **bacilli**. **Cocci** are spherical in shape. **Coccobacilli** have a morphology that is intermediate between that of bacilli and cocci. Finally, **spirochetes** have a corkscrew shape.

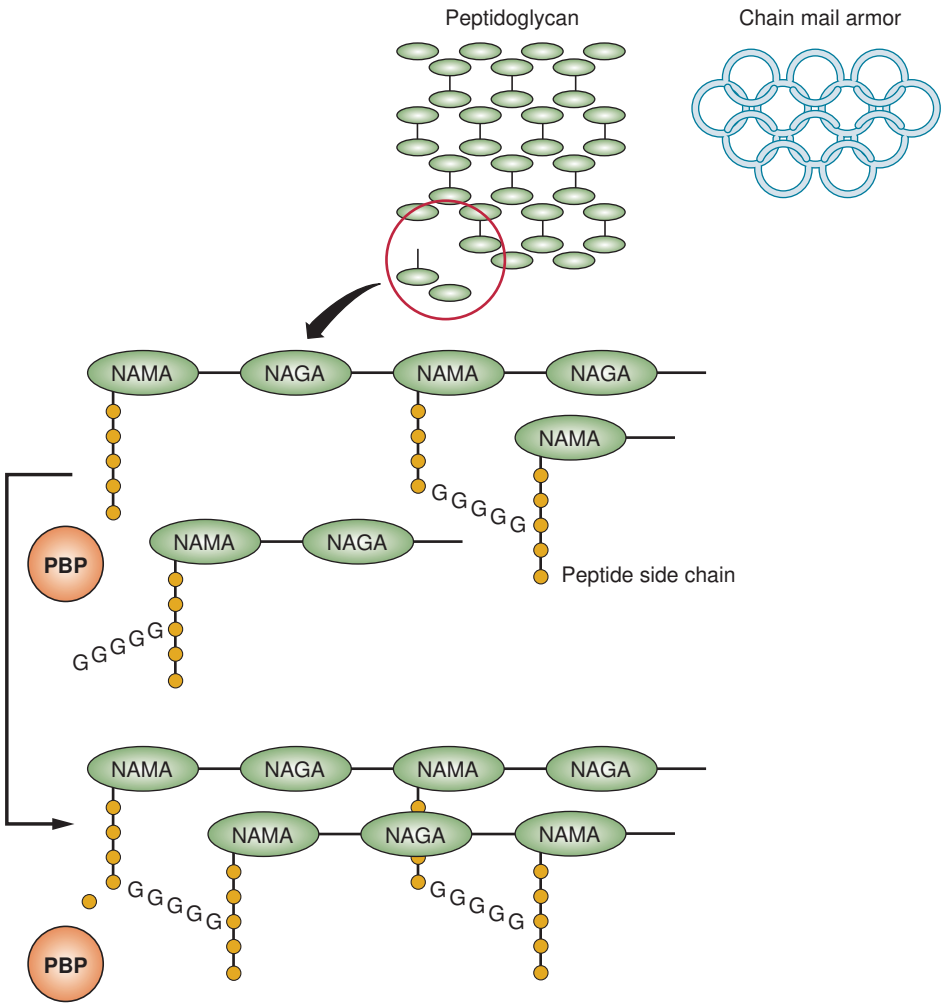

Figure 1-2. Structure of peptidoglycan. Peptidoglycan synthesis requires cross-linking of disaccharide polymers by penicillin-binding proteins (PBPs). *NAMA*, *N*-acetylmuramic acid; *NAGA*, *N*-acetylglucosamine; *GGG*, glycine bridge.

QUESTIONS (Answers to questions are found in Appendix 9.)

1. The bacterial cell wall is composed of _____.

2. _____ are enzymes that cross-link peptidoglycan polymers.

3. _____ are rod-shaped bacteria.

CHAPTER

2

Protein Production

"Plunder fertile country to supply the army with plentiful provisions."

—The Art of War, Sun Tzu

Like all invading armies, bacteria causing an infection need to be resupplied. They require the proper resources to allow for replacement of old worn-out parts and for building new bacteria. Bacteria acquire these resources from the "country" they are invading, which is the human body. Among the most abundant of the synthesized replacement parts are proteins. The synthesis of these proteins is accomplished using the same general processes that are utilized by human cells (Fig. 2-1). First, a number of raw materials or building blocks, such as RNAs, amino acids, and energy-containing nucleoside triphosphates, must be acquired and available within the bacterium. If this condition is met, template bacterial genes are transcribed into RNA by special bacterial enzymes. RNA is then translated into protein. Because some of the bacterial components essential for these processes differ significantly from their human cell counterparts, protein production in bacteria is amenable to inhibition by antibiotics.

RAW MATERIALS

The process of synthesizing new proteins requires abundant amounts of building blocks as well as energy. For example, it is estimated that the energy of three or four nucleoside triphosphates (e.g., adenosine triphosphate [ATP] or guanosine triphosphate [GTP]) is required to add a single amino acid to a growing protein. The bacterium generates these raw materials and energy by taking up fuel sources such as glucose from the environment and processing them through metabolic pathways that harness their energy and generate intermediate compounds.

These metabolic pathways are quite complex and differ significantly between bacteria and human cells. They can be effectively used to divide bacteria into two categories: **aerobes** and **anaerobes**. Aerobic bacteria use oxygen from their environment in the process of metabolism, whereas anaerobic bacteria do not. In fact, strict anaerobes

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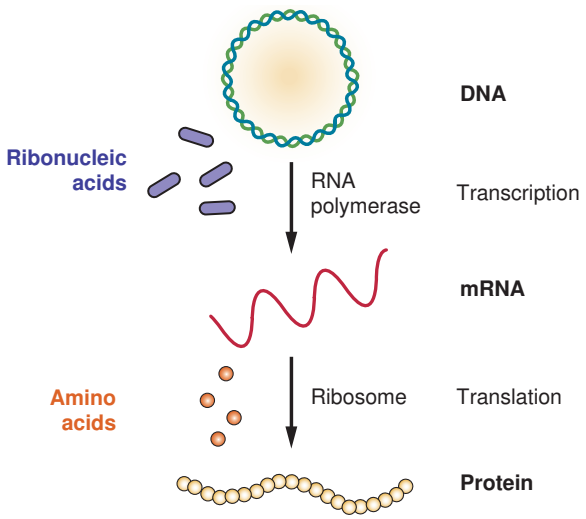

Figure 2-1. An overview of the process by which proteins are produced within bacteria.

are killed by oxygen because they lack enzymes that detoxify some of the harmful by-products of oxygen, such as hydrogen peroxide and superoxide radicals. *Mycobacterium tuberculosis* is an example of a strict aerobic bacterium; strict anaerobic bacteria include *Clostridium difficile* and *Bacteroides fragilis*. Many bacteria have metabolic pathways that allow them to utilize oxygen when it is present but to function as anaerobes when it is absent. These bacteria are said to be **facultative** with respect to oxygen use and obviously survive fine in the presence or absence of oxygen. Examples of such facultative bacteria include *Escherichia coli* and *Staphylococcus aureus*. Other bacteria grow best in the presence of small amounts of oxygen, less than would be found in air. These bacteria are said to be **microaerophilic**. *Campylobacter jejuni* is an example of a microaerophilic bacterium.

The energy available in the fuel consumed by bacteria is harnessed and stored in the form of nucleoside triphosphates and, in some cases, in the generation of a proton gradient between the interior and exterior of the cell. The potential energy stored in this gradient is referred to as the **proton motive force**. As protons flow down this gradient (from outside the bacterium to inside the bacterium) and through the cytoplasmic membrane, this energy is utilized to power important processes such as the active transport of nutrients into the cell and the generation of ATP.

TRANSCRIPTION

Transcription is the process by which the information in the DNA of a bacterial gene is used to synthesize an RNA molecule referred to as **messenger RNA (mRNA)**. As in human cells, the enzyme complex **RNA polymerase** is used by bacteria to accomplish this. RNA polymerase binds to DNA and uses this template to sequentially add ribonucleic acids to a corresponding molecule of mRNA. This process is quite efficient; under ideal conditions, bacterial RNA polymerase can make mRNA at a rate of 55 nucleotides per second.

Although both molecules perform similar functions, bacterial RNA polymerase is quite distinct from eukaryotic RNA polymerase. (Eukaryotes, unlike bacteria, are

organisms that contain nuclei and other membrane-bound organelles within their cells. Examples include animals, plants, fungi, and protozoa.) Structurally, bacterial RNA polymerase consists of five subunits and has overall dimensions of approximately 90 × 90 × 160 angstroms, whereas yeast RNA polymerase has many more subunits and has dimensions of 140 × 136 × 110 angstroms. Functional differences also exist. For example, whereas bacterial RNA polymerase by itself is sufficient to initiate transcription, eukaryotic RNA polymerase requires the help of additional transcription factors. The importance of transcription to the health of the bacterium and the differences between bacterial and eukaryotic RNA polymerases make this enzyme complex an ideal target for antimicrobial compounds.

TRANSLATION

In both eukaryotes and bacteria, macromolecular structures called **ribosomes** do the work of synthesizing proteins from the information present in mRNA, a process called **translation**. These large complexes are composed of both **ribosomal RNA (rRNA)** and proteins. Bacterial ribosomes, however, differ significantly from their eukaryotic counterparts. The **70S bacterial ribosome** is made of a **50S subunit** and a **30S subunit** (Fig. 2-2). ("S" stands for Svedberg units, which are a measure of the rate of sedimentation in an ultracentrifuge. Svedberg units, thus, reflect the size of a complex but are not additive.) These subunits themselves are complex structures. For example, the 50S subunit is made of 2 rRNA molecules and 34 proteins, whereas the 30S subunit consists of 1 rRNA molecule and 21 proteins. In contrast, the eukaryotic ribosome is 80S in size and consists of a 60S subunit and a 40S subunit. Each of these, in turn, is made of multiple rRNA molecules and proteins.

The complete ribosome functions together with another type of RNA, **transfer RNA (tRNA)**, to manufacture new proteins. The ribosome binds to and reads the mRNA template and appropriately incorporates amino acids delivered by the tRNA into the nascent protein based on the information in this template. The importance of translation is indicated by the fact that half of all RNA synthesis in rapidly growing bacteria is devoted to rRNA and tRNA. The essential role played by protein synthesis in bacterial growth and the dissimilarity between the bacterial ribosome and the human ribosome make the former an attractive antibiotic target. Indeed, numerous classes of antimicrobial agents act by binding to and inhibiting the bacterial ribosome.

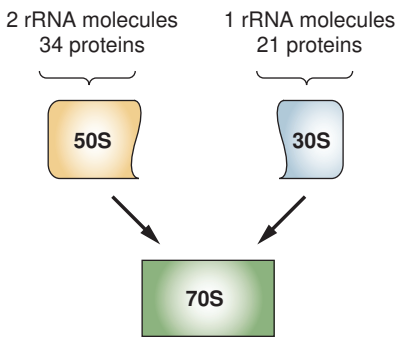

Figure 2-2. Structure of the bacterial ribosome.

Questions

1. _____ bacteria are those that grow in the absence of oxygen.
2. _____ is an enzyme complex that makes mRNA from a DNA template.
3. The 70S bacterial ribosome consists of _____ and _____ subunits, which themselves consist of _____ and _____.

CHAPTER

3

Replication

"We think we have now allotted to the superiority in numbers the importance which belongs to it; it is to be regarded as the fundamental idea, always to be aimed at before all and as far as possible."

—On War, Carl Von Clausewitz

In the battle between bacteria and the human immune response, numbers are key. Bacteria are continuously multiplying in an attempt to overwhelm the host's defensive capabilities, and immune factors are constantly attempting to eradicate the invaders. It is this balance that is often tipped in favor of the human immune response by antibiotics.

An illustrative example of the importance of bacterial multiplication in infection is shigellosis. This form of infectious diarrhea is caused by the bacterium *Shigella* and can occur following ingestion of as few as 200 organisms. Yet, over a short period, these 200 organisms lead to diarrhea in which billions of bacteria are expelled every day in the feces. Obviously, rapid bacterial multiplication is essential for this disease.

Bacterial multiplication occurs by binary fission, the process by which a parent bacterium divides to form two identical daughter cells. This requires the synthesis of numerous biomolecules essential for construction of the daughter cells. Nearly all bacteria have a single circular chromosome, the replication of which is an integral part of cell division. Replication occurs when bacterial enzymes use the existing chromosome as a template for synthesis of a second identical chromosome. To accomplish this, a ready supply of deoxynucleotides must be available for incorporation into the nascent DNA molecule. This process is more complicated than one might suspect, and other enzymes are also required to regulate the conformation of the DNA to allow for optimal replication of the chromosome. These complex processes afford several opportunities for antimicrobial agents to inhibit bacterial growth.

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SYNTHESIS OF DEOXYNUCLEOTIDES

An abundant supply of deoxyadenosine triphosphate (dATP), deoxyguanosine triphosphate (dGTP), deoxycytidine triphosphate (dCTP), and deoxythymidine triphosphate (dTTP) is essential for the production of DNA molecules during DNA replication. Bacteria use several synthetic pathways to manufacture these DNA building blocks. **Tetrahydrofolate (THF)** is an essential cofactor for several of these pathways and is synthesized as follows (Fig. 3-1): The enzyme dihydropteroate synthase uses dihydropterin pyrophosphate and *para*-aminobenzoate (PABA) to generate dihydropteroate, which is subsequently converted to dihydrofolate. Dihydrofolate reductase then converts dihydrofolate into THF. THF is required for the ultimate synthesis of several nucleotides. Although humans readily absorb folate, a precursor of THF, from their diet, most bacteria are unable to do so and must synthesize this cofactor. This synthetic pathway is thus an attractive target for antimicrobial compounds.

DNA SYNTHETIC ENZYMES

The enzyme **DNA polymerase** is responsible for replicating the bacterial chromosome, but other enzymes are also required for this process. One example is the **topoisomerases** that regulate **supercoiling**, or twisting of the DNA. To understand supercoiling, one must appreciate the consequences of having a chromosome composed of helical DNA. The double helix structure of DNA dictates that in a relaxed state, it will contain 10 nucleotide pairs per each helical turn. However, by twisting one end of the DNA while holding the other end fixed, one can increase or decrease the number of nucleotide pairs per helical turn, say to 11 or 9 (Fig. 3-2). This results in additional stress on the DNA molecule, which is accommodated by the formation of supercoils. When there is an increase in the number of nucleotide pairs per helical turn, the supercoiling is said to be positive. When there is a decrease, the supercoiling is said to be negative. An analogous process occurs in bacteria. Because parts of the chromosome are "fixed" due to associations with large protein complexes, twists that occur in one portion cannot freely dissipate but accumulate and form supercoils. So where do the twists come from? RNA polymerase is a large molecule that is unable to spin freely while it moves along the bacterial chromosome during transcription. Thus, as RNA polymerase forges its way along the chromosome, separating the DNA strands as it goes, positive supercoiling occurs in front of the enzyme, whereas negative supercoils accumulate behind it. In theory, excess supercoiling could present a barrier to DNA replication and transcription.

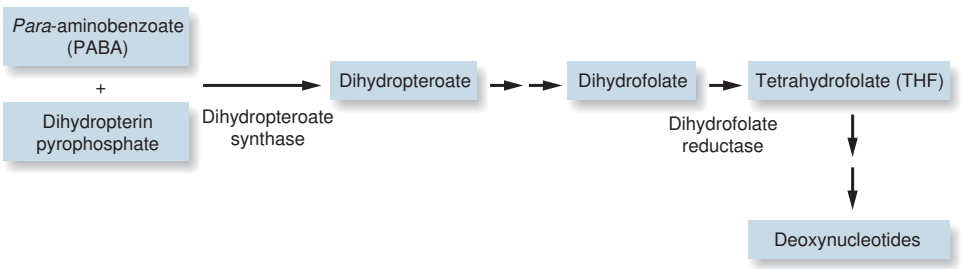


Figure 3-1. Bacterial synthesis of tetrahydrofolate.

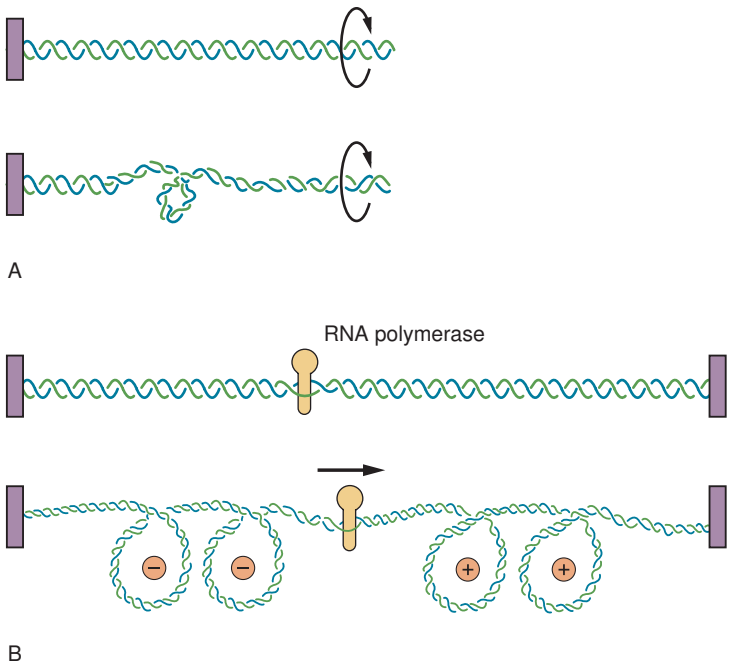


Figure 3-2. Supercoiling of the double helical structure of DNA. **A.** Twisting of DNA results in formation of supercoils. **B.** During transcription, the movement of RNA polymerase along the chromosome results in the accumulation of positive supercoils ahead of the enzyme and negative supercoils behind it. (Adapted from *Molecular Biology of the Cell*, fourth edition by Bruce Alberts, et al. Copyright © 2002 by Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter. Copyright © 1983, 1989, 1994 by Bruce Alberts, Dennis Bray, Julian Lewis, Martin Raff, Keith Roberts, and James D. Watson. Used by permission of W.W. Norton & Company, Inc.)

To visualize supercoiling, hold a coiled telephone cord tightly with your left hand at a point about a foot from the receiver. Now with your right hand, grab the cord at the same point and "strain" the cord through your fingers, moving your hand toward the telephone receiver. In this example, the cord is the helical chromosomal DNA and your right hand is the RNA polymerase moving along the chromosome. Note how supercoils accumulate in the cord ahead of your hand. Now, let the telephone receiver dangle in the air. The weight of the receiver removes the supercoils from the cord, forcing the cord to take on an overly twisted conformation. But the receiver is now no longer fixed, so it can spin freely to relieve this stress.

A second consequence of the circular nature of the bacterial chromosome is that following completion of replication, the two daughter chromosomes will frequently be interlinked (Fig. 3-3). This obviously presents an obstacle for the dividing bacterium while it tries to segregate one chromosome to each of the daughter cells.

Bacteria overcome both these problems by producing topoisomerases, enzymes that remove or add supercoiling to DNA. They do this by binding to the DNA, cutting one or both strands of the DNA, passing either a single strand of DNA or double-stranded DNA through the break, and then re-ligating the DNA. The passage

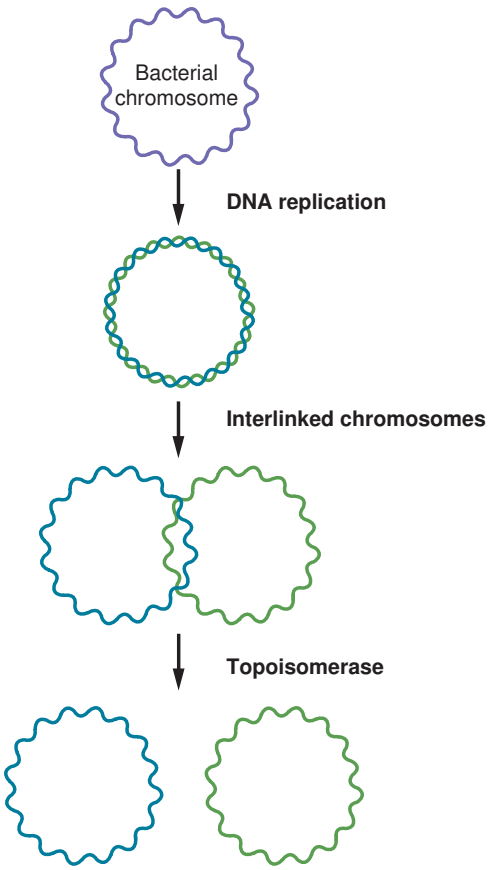


Figure 3-3. Replication of the bacterial chromosome. A consequence of the circular nature of the bacterial chromosome is that replicated chromosomes are interlinked, requiring topoisomerase for appropriate segregation.

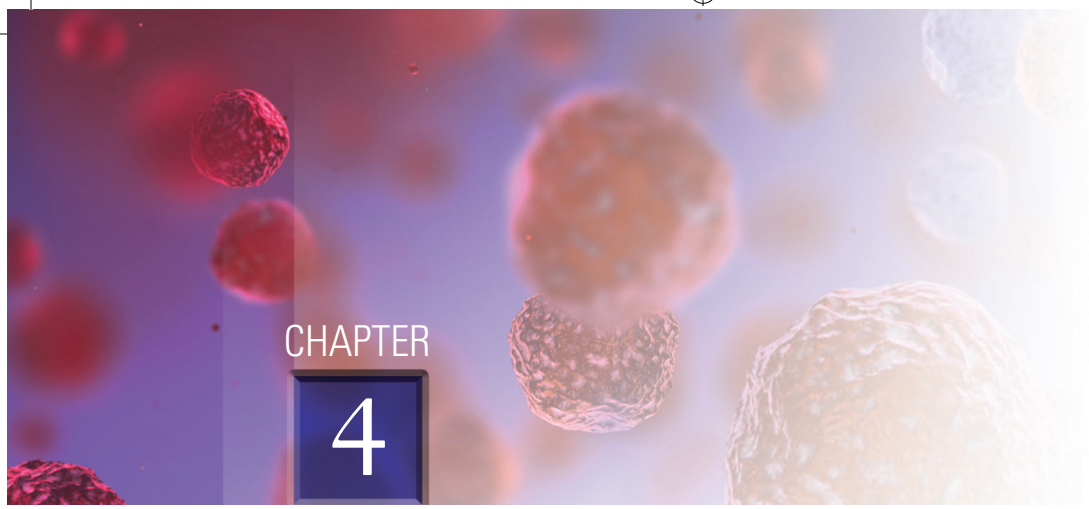
of one or two strands of DNA through the break in essence removes or adds one or two supercoils to the chromosome. It may also unlink two interlocked chromosomes following replication. In this way, bacteria are able to regulate the degree of supercoiling in their chromosomes and allow for separation of chromosomes following DNA replication.

QUESTIONS

1. Tetrahydrofolate is required for several pathways involving the synthesis of _____.

2. The chromosomes of most bacteria are _____.

3. _____are enzymes that regulate DNA supercoiling.



CHAPTER

4

Measuring Susceptibility to Antibiotics

"The best form of defense is attack."

—On War, Carl von Clausewitz

We have now discussed three processes of bacteria that are both essential for their survival and distinct from corresponding human cell processes: generation of the cell envelope, production of bacterial proteins, and replication of the bacterial chromosome. Each of these processes provides multiple targets for antibiotics that inhibit bacteria. Antibiotics can be divided into two classes: Those antibiotics that kill bacteria are called **bactericidal**, and those that merely suppress bacterial growth are called **bacteriostatic**. Bacteriostatic antibiotics rely on the immune system to eradicate the nonmultiplying bacteria from the patient.

The susceptibility of a bacterial isolate to a given antibiotic is quantified by the **minimum inhibitory concentration (MIC)** and the **minimum bactericidal concentration (MBC)**. As its name implies, the MIC measures the minimum concentration of antibiotic that is still able to suppress growth of the bacterial isolate. Likewise, the MBC is the minimum concentration of antibiotic that results in killing of the bacterial isolate.

In practice, several assays have been developed to measure whether any given bacterial isolate is susceptible or resistant to a particular antibiotic. In the **Kirby-Bauer method**, antibiotic-impregnated wafers are dropped onto agar plates streaked with bacteria. The antibiotics diffuse from the wafers, establishing a gradient with lower concentrations occurring further from the wafer. Bacterial growth will be suppressed in a zone surrounding the wafer, and measurement of the diameter of the zone can be used to determine whether the bacterial strain is susceptible or resistant to the antibiotic. **Etests** operate on a similar principle except that an elongated strip is used instead of a wafer. The strip is impregnated with a decreasing gradient of antibiotic

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PEARL

The immune system appears to be relatively ineffective in the eradication of bacteria in certain types of infections, such as meningitis and endocarditis. In these infections, bactericidal antibiotics should be used instead of bacteriostatic antibiotics.

concentrations along its length. When it is dropped onto an agar plate that has been streaked with a lawn of bacteria, the bacteria will grow right up to the end of the strip where little antibiotic is present but will be unable to grow near the end of the strip that contains high concentrations of antibiotics. The spot where the bacterial lawn first touches the strip is used to estimate the MIC, a process facilitated by MIC designations marked onto the strip itself. **Broth dilution methods** operate on a similar principle except that the antibiotic dilutions are created in wells of liquid media rather than in agar. In these assays, the well with the greatest dilution of antibiotic that still does not support the growth of the bacterium identifies the MIC. Today, the microbiology laboratories of most large hospitals rely on machines that utilize these principles to automatically test hundreds of bacterial isolates.

In the following section, we discuss the individual antibiotics that bind to essential bacterial targets as well as the protective mechanisms that have evolved within bacteria to thwart their action.

QUESTIONS

1. _____ antibiotics kill rather than inhibit the growth of bacteria.
2. The _____ method of measuring antibiotic susceptibility utilizes antibiotic impregnated wafers dropped onto an agar plate streaked with a lawn of bacteria.
3. The _____ method of measuring antibiotic susceptibility utilizes serial dilutions of antibiotics in liquid media.

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PART 2

Antibacterial Agents

"The warrior, in accordance with his aims, maintains various weapons and knows their characteristics and uses them well."

—The Book of Five Rings, Miyamoto Musashi

To protect the human body from the onslaught of bacterial pathogens, a large number of antimicrobial compounds have been developed that target points of vulnerability within these invaders. These agents can be grouped into three broad categories based on their mechanism of action: (1) those that target the bacterial cell envelope, (2) those that block the production of new proteins, and (3) those that target DNA or DNA replication.

We now discuss the individual antimicrobial agents. For each, a summary of its antimicrobial spectrum is given in the form of a traffic light. For this purpose, bacteria are broadly grouped into four categories: aerobic gram-positive bacteria, aerobic gram-negative bacteria, anaerobic bacteria, and atypical bacteria. The activity of an antibiotic against a particular category of bacteria is represented by a green light (active), a yellow light (sometimes active), or a red light (not active). Thus, in the example shown in the second figure, one should **go** ahead and use the antibiotic to treat an infection caused by gram-positive bacteria, **stop** if considering using the antibiotic to treat an infection caused by gram-negative bacteria, and proceed with **caution** if treating an infection caused by anaerobic or atypical bacteria. Note that these are only general indications of the antibiotic's activity against these classes of bacteria. There are almost certainly exceptions, and many other factors, such as the antibiotic's ability to achieve high concentrations at the site of the infection, whether it kills or merely inhibits the bacteria, contraindications to the drug, and the patient's antibiotic

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History

Some of the earliest antibacterial agents were antibodies. Serum containing antibodies that bound and inactivated diphtheria toxin was already used to treat individuals with diphtheria in the 1800s. Although most currently used antibiotics are small molecules, antibodies that target toxins made by pathogenic bacteria are experiencing a renaissance. For example, raxibacumab and bezlotoxumab are human monoclonal antibodies that bind a component of *Bacillus anthracis* anthrax toxin and *Clostridium difficile* toxin B, respectively. It is anticipated that antibodies will again play an important role in the treatment of patients with bacterial infections.

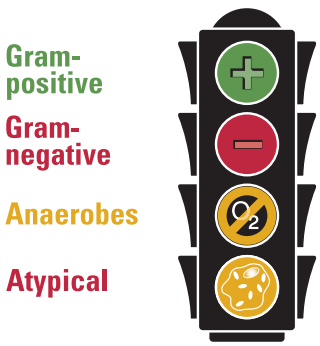
Markham A. Bezlotoxumab: first global approval. *Drugs*. 2016;76:1793–1798.
Migone TS, Subramanian GM, Zhong J, et al. Raxibacumab for the treatment of inhalational anthrax. *N Engl J Med*. 2009;361:135–144.

history, must be taken into account when actually choosing an appropriate agent. Nonetheless, the traffic light representation is useful as a first step in learning the antimicrobial spectra of individual antibiotics.

Groupings of bacteria used in subsequent chapters

	Examples
gram-positive bacteria	*Staphylococcus aureus* *Streptococcus pneumoniae* Enterococci *Listeria monocytogenes*
gram-negative bacteria	*Haemophilus influenzae* *Neisseria* spp. Enterobacteriaceae *Pseudomonas aeruginosa*
anaerobic bacteria	*Bacteroides fragilis* *Clostridium species*
atypical bacteria	*Chlamydia* spp. *Mycoplasma* spp. *Legionella pneumophila*

Traffic sign representation of antimicrobial spectrum of activity



ADDITIONAL READINGS

For excellent overviews of antibiotics, please see these references:

Bennett JE, Dolin R, Blaser MJ. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015.

Mascaretti OA. *Bacteria versus Antibacterial Agents: An Integrated Approach*. Washington, DC: ASM Press; 2003.

Thompson RL, Wright AJ. Symposium on antimicrobial agents, parts I–XVII. *Mayo Clin Proc*. 1998–2000:73–75.

Walsh C. *Antibiotics: Actions, Origins, Resistance*. Washington, DC: ASM Press; 2003.

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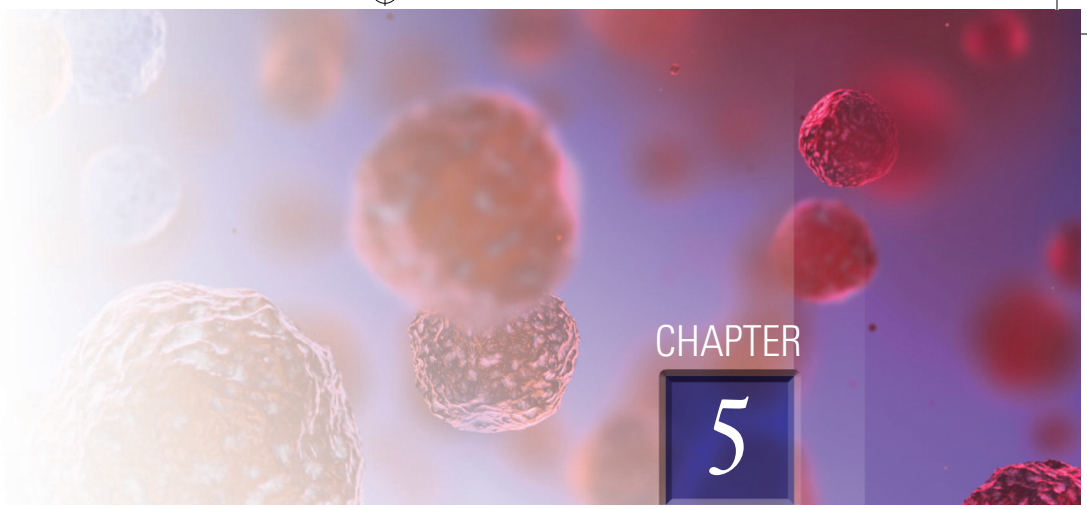

CHAPTER

5

Antibiotics that Target the Cell Envelope

"Though the knights, secure in their heavy armour, had no scruples in riding down and killing the leather-clad foot-soldier, it is entertaining to read of the fierce outcry they made when the foot-soldier retaliated with steel crossbow. . . . The knights called Heaven to witness that it was not honourable warfare to employ such weapons in battle, the fact being that they realized that armour was no longer the protection to their persons which it was before the days of heavy crossbows. . . ."

—The Crossbow, Sir Ralph Payne-Gallwey

If the cell envelope is the bacterium's armor, then β-lactam antibiotics, glycopeptides, daptomycin, and colistin are the crossbows capable of piercing it. These antimicrobial agents attack the protective cell envelope, turning it into a liability for bacterium. In the following sections, we discuss how these antibiotics kill bacteria, the types of bacteria they are active against, and their toxicities.

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β-Lactam Antibiotics

The exciting story of β-lactam antibiotics began in 1928, when Alexander Fleming noticed that a mold contaminating one of his cultures prevented the growth of bacteria. Because the mold was of the genus *Penicillium*, Fleming named the antibacterial substance "penicillin," the first of a long line of β-lactam agents. Characterization of this compound progressed rapidly, and, by 1941, clinical trials were being performed with remarkable success on patients.

The essential core of penicillin is a four-member ring called a **β-lactam ring** (Fig. 5-1). Modifications of this basic structure have led to the development of several useful antibacterial compounds, each with its own characteristic spectrum of activity and pharmacokinetic properties. These include the **penicillins**, **cephalosporins**, **carbapenems**, and **monobactams** (Table 5-1). It is important to remember, however, that the antibacterial activity of each β-lactam compound is based on the same basic mechanism (Fig. 5-2). Although somewhat of an oversimplification, β-lactam antibiotics can be viewed as inhibitors of penicillin-binding proteins (PBPs) that normally assemble the peptidoglycan layer surrounding most bacteria. It has been hypothesized that the β-lactam ring mimics the D-alanyl–D-alanine portion of the peptide side chain that is normally bound by PBPs. PBPs thus interact with the β-lactam ring and are not available for synthesis of new peptidoglycan (Fig. 5-3). The disruption of the peptidoglycan layer leads to lysis of the bacterium.

As is the case with all antibiotics, resistance to β-lactams can be divided into two main categories: intrinsic and acquired. **Intrinsic resistance** refers to a resistance mechanism that is intrinsic to the structure or physiology of the bacterial species. For example, the porins in the outer membrane of all *Pseudomonas aeruginosa* strains do not allow passage of ampicillin to the periplasmic space, and all strains of *P. aeruginosa* are therefore resistant to this antibiotic. In contrast, **acquired resistance** occurs when a bacterium that was previously sensitive to an antibiotic acquires a mutation or exogenous genetic material that allows it to now resist the activity of that antibiotic. For example, most strains of *P. aeruginosa* are susceptible to the carbapenem imipenem, which gains access to the PBPs of this organism by passing through a specific protein channel found in the outer membrane. However, following exposure to imipenem, spontaneous mutations may occur that result in loss of production of this channel. This, in turn, causes acquired resistance to imipenem. Practically speaking, intrinsic resistance usually implies that all strains of a bacterial species are resistant to a given antibiotic, whereas acquired resistance affects only some strains of a bacterial species.

Resistance usually results from failure of an agent to avoid one of six potential **P**itfalls in the process by which β-lactam antibiotics cause bacterial pathogens

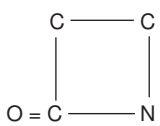


Figure 5-1. The structure of the β-lactam ring.

Table 5-1	β-Lactam Antibiotics
Penicillins	
Cephalosporins	
Carbapenems	
Monobactams	

to perish (Fig. 5-4). These are the six **P**s: (1) **P**enetration—β-lactams penetrate poorly into the intracellular compartment of human cells, so bacteria that reside in this compartment are not exposed to them. A β-lactam antibiotic cannot kill a bacterium if it cannot get to it. (2) **P**orins—if a β-lactam antibiotic does reach the bacterium, it must gain access to its targets, the PBPs. In gram-positive bacteria,

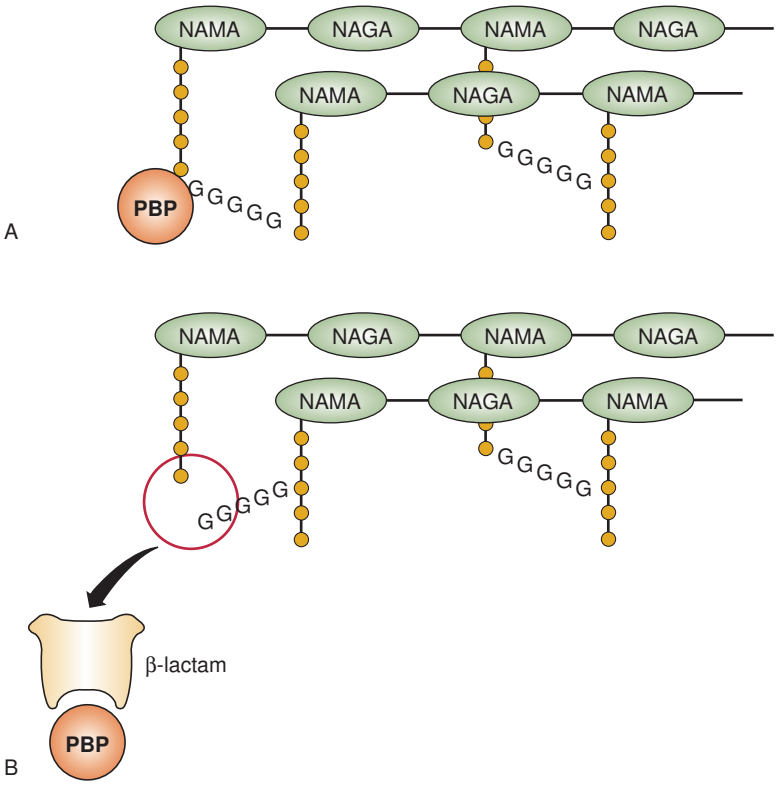


Figure 5-2. Mechanism of action of β-lactam antibiotics. **A.** Normally, a new subunit of *N*-acetylmuramic acid (NAMA) and *N*-acetylglucosamine (NAGA) disaccharide with an attached peptide side chain is linked to an existing peptidoglycan polymer. This may occur by covalent attachment of a glycine (G) bridge from one peptide side chain to another through the enzymatic action of a PBP. **B.** In the presence of a β-lactam antibiotic, this process is disrupted. The β-lactam antibiotic binds the PBP and prevents it from cross-linking the glycine bridge to the peptide side chain, thus blocking incorporation of the disaccharide subunit into the existing peptidoglycan polymer.

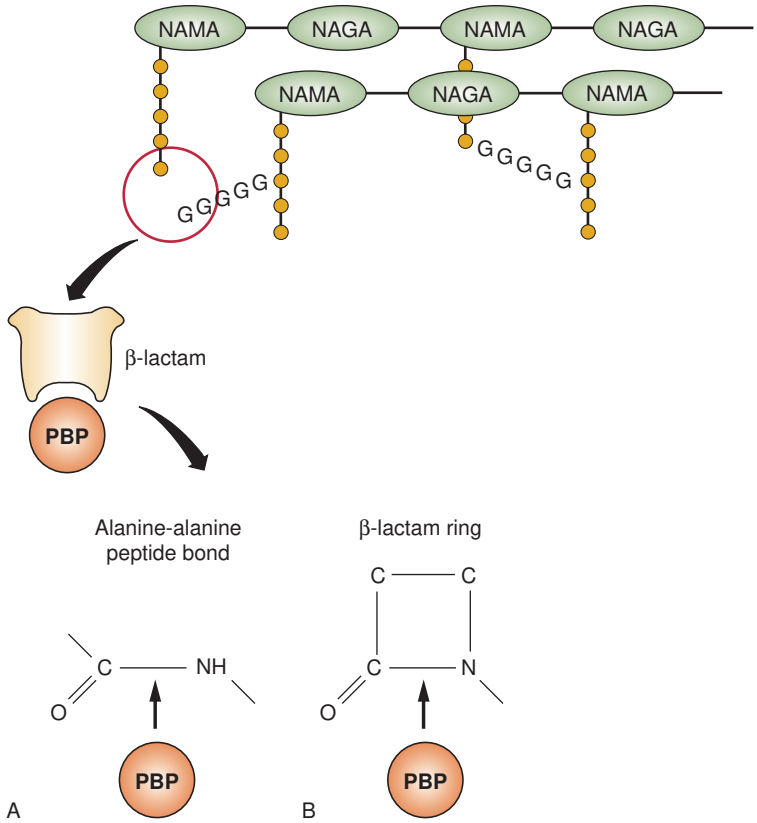


Figure 5-3. Mechanism of penicillin-binding protein (PBP) inhibition by β-lactam antibiotics. **A.** PBPs recognize and catalyze the peptide bond between two alanine subunits of the peptidoglycan peptide side chain. **B.** The β-lactam ring mimics this peptide bond. Thus, the PBPs attempt to catalyze the β-lactam ring, resulting in inactivation of the PBPs.

this is not difficult because the PBPs and the peptidoglycan layer are relatively exposed, but in gram-negative bacteria, they are surrounded by the protective outer membrane. β-Lactams must breach this membrane by diffusing through porins, which are protein channels in the outer membrane. Many gram-negative bacteria have porins that do not allow passage of certain β-lactams to the periplasmic space. (3) **P**umps—some bacteria produce **efflux pumps**, which are protein complexes that transport antibiotics that have entered the periplasmic space back out to the environment. These pumps prevent antibiotics from accumulating within the periplasm to concentrations sufficient for antibacterial activity. (4) **P**enicillinases (really β-lactamases, but that does not start with P)—many bacteria, both gram-positive and gram-negative, make **β-lactamases**, enzymes that degrade β-lactams before they reach the PBPs. (5) **P**BPs—some bacteria produce PBPs that do not bind β-lactams with high affinity. In these bacteria, β-lactams reach their targets, the PBPs, but cannot inactivate them. (6) **P**eptidoglycan is absent—there are a few bacteria

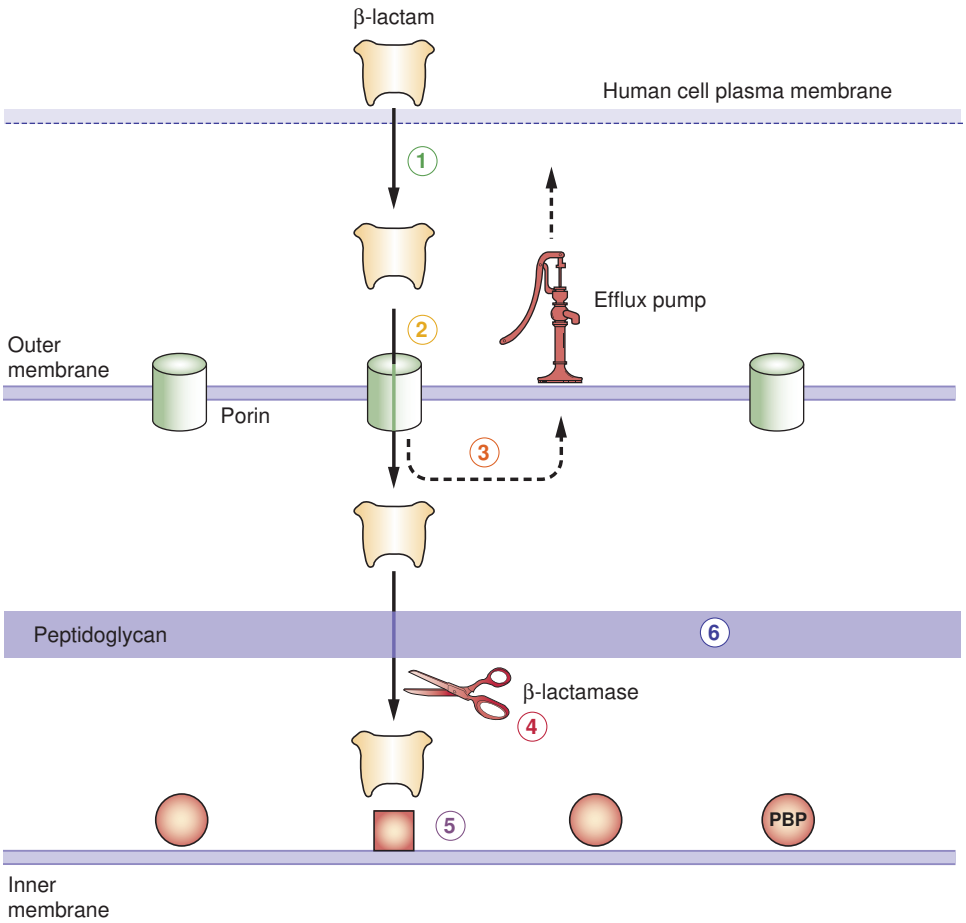
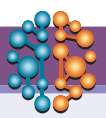


Figure 5-4. Six Ps by which the action of β-lactams may be blocked: **(1)** penetration, **(2)** porins, **(3)** pumps, **(4)** penicillinases (β-lactamases), **(5)** penicillin-binding proteins (PBPs), and **(6)** peptidoglycan.

that do not make peptidoglycan and that therefore are not affected by β-lactams. To be effective, β-lactam agents must successfully navigate around each of these potential pitfalls. It is important to note that β-lactam antibiotics are a heterogeneous group of compounds; some may be blocked at certain steps through which others may proceed without difficulty.



REMEMBER

Remember the six **P**s of resistance to β-lactam antibiotics: **P**enetration, **P**orins, **P**umps, **P**enicillinases, **P**BPs, absent **P**eptidoglycan.

History

It was originally thought that antibiotic resistance first occurred as bacteria responded to the therapeutic use of antibiotics in the 20th century. It is now clear that antibiotic resistance genes are thousands of years old and likely evolved along with environmental microbes that naturally produced antimicrobial compounds.

D'Costa VM, King CE, Kalan L, et al. Antibiotic resistance is ancient. *Nature*. 2011;477:457–461.

One point about β-lactamases: They come in many flavors—that is to say that some are specific for a few β-lactam antibiotics, whereas others have activity against nearly all β-lactam agents. For example, the β-lactamase of *Staphylococcus aureus* is relatively specific for some of the penicillins, whereas the extended-spectrum β-lactamases made by some strains of *Escherichia coli* and *Klebsiella* spp. (abbreviation for the plural of species) degrade nearly all penicillins, cephalosporins, and monobactams. Different species or strains of bacteria produce different types of β-lactamases that confer upon them unique antibiotic resistance patterns. Thus, generalizations about β-lactamases and their effects on specific antibiotics must be made with caution.

Despite their many limitations, β-lactam antibiotics remain some of the most powerful and broad-spectrum antibiotics available today. They comprise a significant proportion of the total antibiotics prescribed every year.

Questions

1. All β-lactam antibiotics act by preventing proper construction of the bacterial _____ layer.

2. The four major classes of β-lactam antibiotics are _____, _____, _____, and _____.

3. All β-lactam antibiotics exert their action by binding to _____.

4. _____ are enzymes that cleave β-lactam antibiotics, thus inactivating them.

History

By chance, Alexander Fleming took a 2-week vacation immediately after inoculation of his soon-to-be contaminated agar plates. Because he knew he would not be able to examine the plates for 2 weeks, he incubated them at room temperature instead of 37°C to slow the growth rate of the bacteria. His vacation changed the course of human events. *Penicillium* grows at room temperature but not at 37°C—had Fleming not taken a vacation, he never would have observed the bactericidal effects of the mold. So, vacations truly do make one more productive at work.

Friedman M, Friedman GW. *Medicine's Ten Greatest Discoveries*. New Haven, CT: Yale University Press; 1998.

Penicillins

The penicillins each consist of a thiazolidine ring attached to a β-lactam ring that is itself modified by a variable side chain ("R" in Fig. 5-5). Whereas the thiazolidine–β-lactam ring is required for antibacterial activity, the side chain has been manipulated to yield many penicillin derivatives that have altered pharmacologic properties and antibacterial spectra of activity.

As a result of modifications to the R side chain, penicillins come in several classes: the **natural penicillins**, the **antistaphylococcal penicillins**, the **aminopenicillins**, and the **extended-spectrum penicillins** (Table 5-2). In addition, some of the penicillins have been combined with **β-lactamase inhibitors**, which markedly expand the number of bacterial species that are susceptible to these compounds. The members of each class share similar pharmacokinetic properties and spectra of activity but may be quite distinct from members of other classes.

NATURAL PENICILLINS

The natural penicillins, **penicillin G** and **penicillin V**, are the great grandparents of the penicillin antibiotic family but still have much to say about the treatment of antibacterial infections. They are called *natural* penicillins because they can be purified directly from cultures of *Penicillium* mold. The R side chain of penicillin G is shown in Figure 5-6 and consists of a hydrophobic benzene ring.

Because nearly all bacteria have cell walls composed of peptidoglycan, it is not surprising that the natural penicillins are active against some species of gram-positive, gram-negative, and anaerobic bacteria as well as some spirochetes. Despite this broad range of activity, most bacteria are either intrinsically resistant or have now acquired resistance to the natural penicillins. Understanding the reasons for this can help one remember which species remain susceptible. In turn, the bacterial spectra of the natural penicillins can be used as a foundation for remembering the spectra of the other classes of penicillins. The six **P**s explain resistance to the natural penicillins: (1) **P**enetration—natural penicillins, like most β-lactams, penetrate poorly into the intracellular compartment of human cells, so bacteria that for the most part reside in this compartment, such as *Rickettsia* and *Legionella*, are protected from them. (2) **P**orins—some gram-negative bacteria, such as *E. coli*, *Proteus mirabilis*,

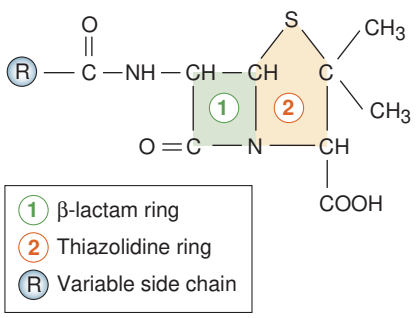


Figure 5-5. The structure of penicillins.

Table 5-2 The Penicillins

Category	Parenteral Agents	Oral Agents
Natural penicillins	Penicillin G	Penicillin V
Antistaphylococcal penicillins	Nafcillin, oxacillin	Dicloxacillin
Aminopenicillins	Ampicillin	Amoxicillin, ampicillin
Aminopenicillins + β-lactamase inhibitors	Ampicillin-sulbactam	Amoxicillin-clavulanate
Extended-spectrum penicillins	Piperacillin, ticarcillin	
Extended-spectrum penicillins + β-lactamase inhibitors	Piperacillin-tazobactam, ticarcillin-clavulanate	

Salmonella enterica, and *Shigella* spp., have porins in their outer membranes that do not allow passage of the hydrophobic natural penicillins to the periplasmic space. (3) **P**umps—some gram-negative bacteria, such as *P. aeruginosa*, have efflux pumps that prevent the accumulation of penicillins within the periplasm. Although these pumps by themselves may only cause a marginal change in susceptibility, they can work together with penicillinases and porins to have a dramatic effect. (4) **P**enicillinases—many bacteria, both gram-positive (staphylococci) and gram-negative (some *Neisseria* and *Haemophilus* strains, many enteric species and some anaerobes, such as *Bacteroides fragilis*), make penicillinases that degrade the natural penicillins. (5) **P**BPs—some bacteria produce PBPs that do not bind natural penicillins with a high affinity (e.g., some strains of *Streptococcus pneumoniae*). (6) **P**eptidoglycan—some bacteria, such as *Mycoplasma*, do not make peptidoglycan and therefore are not affected by the natural penicillins.

Despite these limitations, natural penicillins are still used to treat infections caused by some gram-positive bacteria, especially the streptococci, some anaerobic bacteria, and some spirochetes (Table 5-3). Even a few gram-negative bacteria, such as *Neisseria meningitidis* and some strains of *Haemophilus influenzae* that do not make β-lactamases, remain susceptible to penicillin.

ANTISTAPHYLOCOCCAL PENICILLINS

The antistaphylococcal penicillins (also called the "penicillinase-resistant penicillins") have bulky residues on their R side chains that prevent binding by the staphylococcal β-lactamases (Fig. 5-7). As a result, these penicillins are useful in treating infections caused by *S. aureus* and *Staphylococcus epidermidis*. However, they are unable to bind the PBPs of two special groups of staphylococci called methicillin-resistant

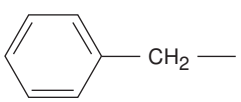


Figure 5-6. R side chain of penicillin G.

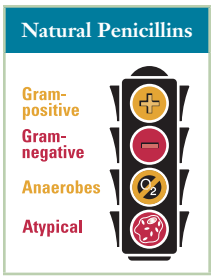


Table 5-3 Antimicrobial Activity of Natural Penicillins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans group streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) *Actinomyces israelii*
Spirochetes	*Treponema pallidum* *Leptospira* spp.

S. aureus (MRSA) and methicillin-resistant *S. epidermidis* (MRSE). Because they cannot bind the PBPs of MRSA and MRSE bacteria, antistaphylococcal penicillins are inactive against them. (Note that methicillin is an antistaphylococcal penicillin that is no longer commercially available but is representative of the entire class of antistaphylococcal penicillins in its spectrum of activity.) Antistaphylococcal penicillins are also less effective than natural penicillins against streptococci and are usually not used to treat them. Nor are these penicillins active against enterococci. Likewise, the bulkiness of the side chains limits the ability of these agents to penetrate most other bacteria, and they are generally only used to treat staphylococcal infections (Table 5-4). This group of antibiotics includes **nafcillin**, **oxacillin**, and **dicloxacillin**.

AMINOPENICILLINS

The aminopenicillins, **ampicillin** and **amoxicillin**, have spectra of activity similar to the natural penicillins with one exception: An additional amino group in their side chain increases their hydrophilicity and allows them to pass through the porins in the outer membranes of some enteric gram-negative rods, such *E. coli*, *P. mirabilis*, *S. enterica*, and *Shigella* spp. (Fig. 5-8). This extends the spectra of the aminopenicillins to include these bacteria. Aminopenicillins, however, share the natural penicillins' vulnerability

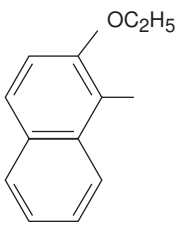


Figure 5-7. R side chain of nafcillin.

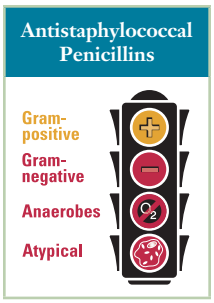


Table 5-4 Antimicrobial Activity of the Antistaphylococcal Penicillins

Gram-positive bacteria	Some *Staphylococcus aureus* Some *Staphylococcus epidermidis*

to β-lactamases, and many of the gram-negative bacteria that were initially susceptible to the aminopenicillins are now resistant due to the acquisition of β-lactamase encoding genes (Table 5-5).

AMINOPENICILLIN/β-LACTAMASE INHIBITOR COMBINATIONS

Compounds have been developed to inhibit the β-lactamases of many gram-positive and gram-negative bacteria. These inhibitors are structurally similar to penicillin and therefore bind β-lactamases, which results in the inactivation of the β-lactamases. Two of these inhibitors, clavulanate and sulbactam, are used in conjunction with the aminopenicillins to greatly expand their spectra of activity. **Ampicillin-sulbactam** is the parenteral formulation and **amoxicillin-clavulanate** is the oral formulation of these combinations. Sulbactam and clavulanate inactivate the β-lactamases of many gram-positive, gram-negative, and anaerobic bacteria. As a result, they dramatically broaden the antimicrobial spectrum of the aminopenicillins (Table 5-6).

EXTENDED-SPECTRUM PENICILLINS

The extended-spectrum penicillins consist of **piperacillin** and **ticarcillin**. The side chains of these agents allow for even greater penetration into gram-negative bacteria than is seen with the aminopenicillins. For example, the side chain of piperacillin is polar, which increases its ability to pass through the outer membrane porins of some gram-negative bacteria (Fig. 5-9). (Incidentally, piperacillin got its name from its side chain, which contains a piperazine derivative.) In addition, the extended-spectrum penicillins are in general more resistant to cleavage by gram-negative β-lactamases than are aminopenicillins, although they remain susceptible to some of these enzymes. Thus, compared to the aminopenicillins, the extended-spectrum penicillins are more

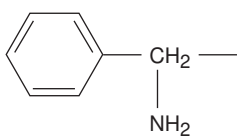


Figure 5-8. R side chain of ampicillin.

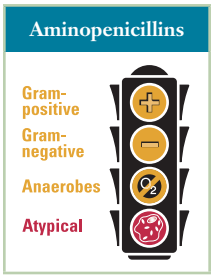


Table 5-5 Antimicrobial Activity of Aminopenicillins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae* Some *Enterobacteriaceae*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) *Actinomyces israelii*
Spirochetes	*Borrelia burgdorferi*

active against gram-negative bacilli, including many strains of *P. aeruginosa*. They maintain some of the gram-positive activity of the natural penicillins but, like the natural penicillins, are susceptible to the β-lactamases of staphylococci. They have modest activity against anaerobes (Table 5-7). Piperacillin has broader activity than ticarcillin.

EXTENDED-SPECTRUM PENICILLIN/β-LACTAMASE INHIBITOR COMBINATIONS

The fullest antimicrobial potential of the penicillins has been achieved by combining extended-spectrum penicillins with β-lactamase inhibitors. The two available combinations are **piperacillin-tazobactam** and **ticarcillin-clavulanate**. The β-lactamase

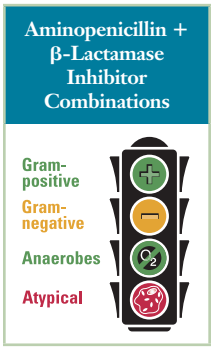


Table 5-6 Antimicrobial Activity of Aminopenicillin + β-Lactamase Inhibitor Combinations

Gram-positive bacteria	Some *Staphylococcus aureus* *Streptococcus pyogenes* Viridans streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria* spp. *Haemophilus influenzae* Many *Enterobacteriaceae*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) *Actinomyces israelii* *Bacteroides* spp.
Spirochetes	*Borrelia burgdorferi*

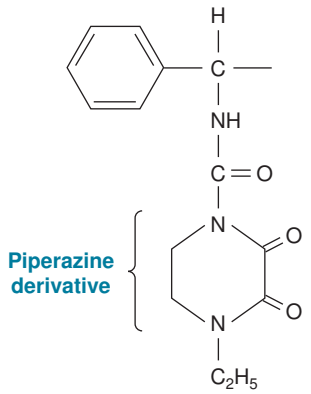


Figure 5-9. R side chain of piperacillin.

inhibitors neutralize many of the β-lactamases that otherwise inactivate the extended-spectrum penicillins, resulting in a marked enhancement of their activity. Thus, piperacillin-tazobactam and ticarcillin-clavulanate are the decathletes of the penicillins, with activity against most aerobic gram-positive bacteria, including many β-lactamase–producing staphylococci, most aerobic gram-negative bacteria, and nearly all anaerobic bacteria except *Clostridium difficile* (Table 5-8). As would be expected based on the activity of their penicillin components, piperacillin-tazobactam has a broader spectrum than ticarcillin-clavulanate. Its excellent activity against gram-positive, gram-negative, and anaerobic bacteria makes piperacillin-tazobactam one of the most powerful antibiotics available today. Ticarcillin-clavulanate is no longer available in the United States.

TOXICITY

Adverse reactions to the penicillins are relatively common; an estimated 3% to 10% of people are allergic to these agents. Like most antibiotics, penicillins can cause nausea, vomiting, and diarrhea. They also have been associated with drug fever, rash, serum sickness, interstitial nephritis, hepatotoxicity, neurologic toxicity, and

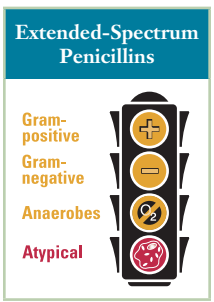


Table 5-7 Antimicrobial Activity of Extended-Spectrum Penicillins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans streptococci Some *Streptococcus pneumoniae* Some enterococci
Gram-negative bacteria	*Neisseria meningitidis* Some *Haemophilus influenzae* Some *Enterobacteriaceae* *Pseudomonas aeruginosa*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) Some *Bacteroides* spp.

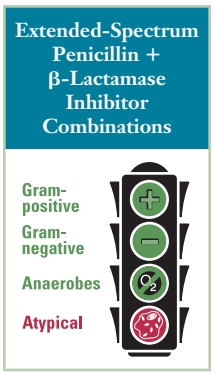
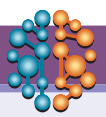


Table 5-8 Antimicrobial Activity of Extended-Spectrum Penicillin + β-Lactamase Inhibitor Combinations

Gram-positive bacteria	Some *Staphylococcus aureus* *Streptococcus pyogenes* Viridans streptococci Some *Streptococcus pneumoniae* Some enterococci *Listeria monocytogenes*
Gram-negative bacteria	*Neisseria* spp. *Haemophilus influenzae* Most *Enterobacteriaceae* *Pseudomonas aeruginosa*
Anaerobic bacteria	*Clostridia* spp. (except *C. difficile*) *Bacteroides* spp.

hematologic abnormalities. Urticaria, angioedema, and anaphylaxis occur and are referred to as immediate hypersensitivity reactions. Of these, the most feared is anaphylaxis, which is rare but life threatening. Persons allergic to one penicillin should be considered allergic to all penicillins, and cross-allergenicity may extend to other β-lactam antibiotics.

The penicillins vary markedly in their activities, especially against gram-negative bacteria. The activities of these agents against gram-negative bacteria can be summarized as follows: (1) The antistaphylococcal penicillins are inactive against gram-negative bacteria. (2) The natural penicillins have activity against *N. meningitidis* and some strains of *H. influenza*, but few on other gram-negative bacteria. (3) The spectrum of the aminopenicillins is expanded to include these organisms plus some enteric gram-negative rods, such as certain strains of *E. coli*, *P. mirabilis*, *S. enterica*, and *Shigella* spp. that do not produce β-lactamases. (4) The extended-spectrum penicillins are active against even more enteric gram-negative rods and, importantly, *P. aeruginosa*. (5) Finally, the addition of a β-lactamase inhibitor to an extended-spectrum penicillin extends this list to include most enteric gram-negative bacilli.



REMEMBER

Penicillin G and penicillin V: Which is oral and which is parenteral?

The letters in penicillin G and penicillin V can be used to remember how these agents are usually administered. Although not actually true, pretend that the "G" in penicillin G means that this drug is destroyed in the stomach ("gastric") and that the "V" in penicillin V means that this drug is destroyed in "veins." Therefore, penicillin G is given intravenously and penicillin V is given orally.

QUESTIONS

5. Penicillins all share the same basic structure, which consists of a thiazolidine ring linked to a _____ with a modifiable _____.
6. Penicillins act by binding _____, which are bacterial enzymes that function to assemble _____.
7. Natural penicillins have moderate activity against aerobic gram-positive bacteria and anaerobic bacteria but poor activity against aerobic _____ bacteria and most atypical bacteria.
8. Antistaphylococcal penicillins are useful in treating infections caused by _____.
9. Compared to natural penicillins, aminopenicillins have improved activity against _____.
10. Addition of a β-lactamase inhibitor to an aminopenicillin expands the spectra of these agents to include many _____ as well as additional _____ and anaerobes.
11. Compared to aminopenicillins, extended-spectrum penicillins have improved activity against aerobic _____, including _____.
12. When used in combination with β-lactamase inhibitors, extended-spectrum penicillins are among the most powerful antibacterial agents available today, and are active against most aerobic _____, aerobic _____, and _____.

ADDITIONAL READINGS

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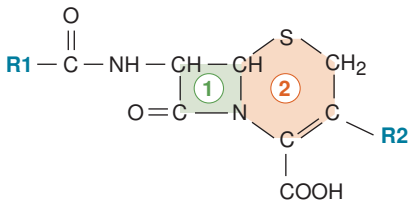
Cephalosporins

The cephalosporins received their name from the fungus *Cephalosporium acremonium*, which was the source of the first members of this class. Even more so than penicillins, these agents constitute a large extended family of antibiotics within the β-lactam group. As such, they are appropriately categorized by "generation." Because agents in each generation have somewhat similar spectra of activity, this organizational scheme is helpful in remembering the properties of the many cephalosporins.

Each cephalosporin is composed of a nucleus with two side chains (Fig. 5-10). The nucleus is 7-aminocephalosporanic acid, which is similar to the nucleus of penicillin except that the β-lactam ring is fused to a six-member dihydrothiazine ring instead of a



1 β-lactam ring
2 Dihydrothiazine ring
R1 Side chain of the β-lactam ring
R2 Side chain of the dihydrothiazine ring

Figure 5-10. The structure of cephalosporins.

five-member thiazolidine ring (compare Fig. 5-10 to Fig. 5-5). The cephalosporin core has two major advantages over the penicillin core: (1) It is intrinsically more resistant to cleavage by β-lactamases and (2) it has two sites, R1 and R2, at which it can be modified. This in part explains the large number of cephalosporins commercially available today.

Like other β-lactam antibiotics, the cephalosporins exert their effects by attaching to and inhibiting PBPs, thereby preventing the appropriate synthesis of peptidoglycan. Although peptidoglycan is a constituent of most bacteria, cephalosporins are not active against certain species and strains of bacteria. As was the case for penicillins, the six **P**s explain resistance to cephalosporins: (1) **P**enetration—cephalosporins, like most β-lactams, penetrate poorly into the intracellular compartment of human cells, so bacteria that for the most part reside in this compartment, such as *Rickettsia* and *Legionella*, are protected from them. (2) **P**orins—some gram-negative bacteria, such as *P. aeruginosa*, have porins in their outer membranes that do not allow passage of many cephalosporins into the periplasmic space. (3) **P**umps—some bacteria, such as *P. aeruginosa*, use efflux pumps to remove antibiotics from the periplasmic space. (4) **P**enicillinases (actually β-lactamases)—many gram-negative bacteria, such as *Enterobacter* and *Citrobacter* spp., make β-lactamases that degrade many cephalosporins. (5) **P**BPs—some bacteria, such as the enterococci and *Listeria monocytogenes*, produce PBPs that do not bind most cephalosporins with a high affinity. (6) **P**eptidoglycan—some bacteria such as *Mycoplasma* do not make peptidoglycan and therefore are not affected by the cephalosporins.

Several generalizations about the spectra of activity of cephalosporins can be made. First, with the exception of the new fifth-generation agents, each successive generation of agents has broader activity against aerobic gram-negative bacteria. Second, also with several important exceptions, cephalosporins have limited activity against anaerobes. Third, the activities of these agents against aerobic gram-positive bacteria are variable, with the fifth-generation agent ceftaroline having the strongest activity against these bacteria.

FIRST-GENERATION CEPHALOSPORINS

Commonly used first-generation cephalosporins include **cefadroxil** and **cefazolin** (Table 5-9). All agents in this group share similar activities against the different types of bacteria.

Table 5-9 The Cephalosporins

Generation	Parenteral Agents	Oral Agents
First generation	Cefazolin	Cefadroxil, cephalexin
Second generation	Cefotetan[a], cefoxitin[a], cefuroxime	Cefaclor, cefprozil, cefuroxime axetil
Third generation	Cefotaxime, ceftazidime, ceftriaxone	Cefdinir, cefditoren, cefpodoxime proxetil, ceftibuten, cefixime
Fourth generation	Cefepime	
Fifth generation	Ceftaroline	
Cephalosporin + β-lactamase inhibitor combinations	Ceftazidime-avibactam Ceftolozane-tazobactam	

[a]Cephamycins

The strength of the first-generation cephalosporins is their activity against aerobic gram-positive cocci such as staphylococci and streptococci (Table 5-10). The R1 side chains of these agents protect their β-lactam rings from cleavage by the staphylococcal β-lactamase (Fig. 5-11). As a result, they are useful in the treatment of infections caused by many strains of *S. aureus*. First-generation cephalosporins cannot bind the PBPs of MRSA and MRSE or many highly penicillin-resistant *S. pneumoniae*; these agents are ineffective against these bacteria. As mentioned previously, most cephalosporins also lack activity against *L. monocytogenes* and the enterococci.

First-generation cephalosporins have limited activity against aerobic and facultative gram-negative bacteria, primarily because the side chains of these agents, although capable of protecting the β-lactam ring from cleavage by staphylococcal β-lactamases, do not afford protection from the β-lactamases of most gram-negative bacteria. Nonetheless, some strains of *E. coli*, *Klebsiella pneumoniae*, and *P. mirabilis* are susceptible.

First-generation cephalosporins have moderate to poor activity against anaerobes, intracellular bacteria, and spirochetes.

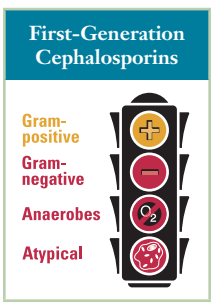


Table 5-10 Antimicrobial Activity of First-Generation Cephalosporins

Gram-positive bacteria	*Streptococcus pyogenes* Some viridans streptococci Some *Staphylococcus* aureus Some *Streptococcus pneumoniae*
Gram-negative bacteria	Some *Escherichia coli* Some *Klebsiella pneumoniae* Some *Proteus mirabilis*

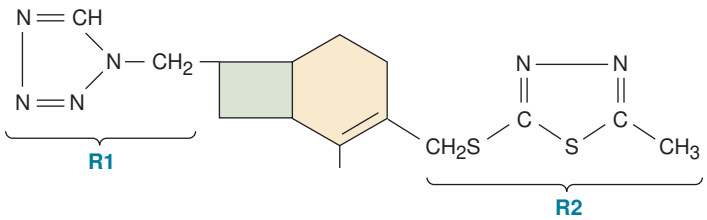


Figure 5-11. Structure of cefazolin.

SECOND-GENERATION CEPHALOSPORINS

Second-generation cephalosporins are divided into two groups: the true cephalosporins, such as **cefuroxime**, and the cephamycins, which include **cefotetan** and **cefoxitin** (see Table 5-9). The cephamycins are derivatives of a parent compound originally isolated from the bacterium *Streptomyces lactamdurans* instead of the fungus *C. acremonium*. They have a methoxy group in place of the hydrogen on the β-lactam ring of the cephalosporin core (Fig. 5-12). Thus, these agents are not actually cephalosporins but are included in this group because they are chemically and pharmacologically similar.

Individual second-generation cephalosporins differ in their activity against aerobic gram-positive bacteria (Table 5-11). The true cephalosporins are in general as active against aerobic gram-positive cocci as the first-generation agents. The cephamycins (cefotetan and cefoxitin) have relatively limited activity against this group of bacteria. The strength of the second-generation agents is their increased activity against aerobic and facultative gram-negative bacteria. Second-generation agents are more potent against *E. coli*, *K. pneumoniae*, and *P. mirabilis* than first-generation agents and are also active against *Neisseria* spp. and, in the case of the true cephalosporins, *H. influenzae* (including β-lactamase-producing strains). Because of the additional methoxy group on the β-lactam ring (Fig. 5-12), the cephamycins also have enhanced stability to the β-lactamases of some anaerobes, such as *B. fragilis*. However, this added anaerobic activity comes at a cost; it is the methoxy group that results in the diminished activity of the cephamycins against staphylococci and streptococci because of decreased affinity for the PBPs of these bacteria.

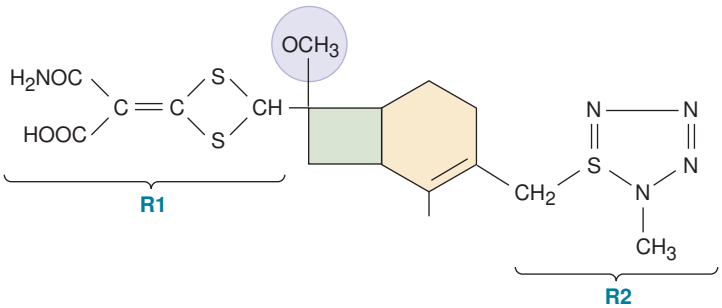


Figure 5-12. Structure of cefotetan. The methoxy group characteristic of the cephamycins is circled.

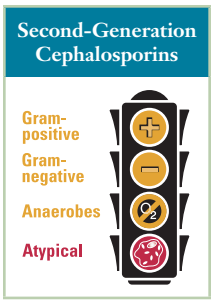


Table 5-11 Antimicrobial Activity of Second-Generation Cephalosporins

Gram-positive bacteria	True cephalosporins have activity equivalent to first-generation agents Cefoxitin and cefotetan have little activity
Gram-negative bacteria	Some Escherichia coli Some *Klebsiella pneumoniae* *Proteus mirabilis* *Haemophilus influenzae* *Neisseria* spp.
Anaerobic bacteria	Cefoxitin and cefotetan have moderate anaerobic activity

THIRD-GENERATION CEPHALOSPORINS

Commonly used third-generation cephalosporins include **ceftriaxone**, **cefotaxime**, and **ceftazidime** (see Table 5-9). In general, compounds in this group have moderate activity against aerobic gram-positive bacteria (Table 5-12) and inhibit most strains of penicillin-susceptible *S. pneumoniae*. Third-generation cephalosporins are also active against the spirochete *Borrelia burgdorferi* but have little activity against anaerobic bacteria.

A modification common to many of the third-generation cephalosporins is the use of an aminothiazolyl group at R1 (Fig. 5-13). The presence of this structure at R1 results in increased penetration of these agents through the bacterial outer membrane, increased affinity for PBPs, and increased stability in the presence of some of the plasmid-encoded β-lactamases of aerobic and facultative gram-negative bacteria. Thus, these agents have enhanced activity against *E. coli*, *Klebsiella* spp., *Proteus* spp., *Neisseria* spp., and *H. influenzae* relative to the second-generation cephalosporins, although many strains of *E. coli* and *Klebsiella* have acquired β-lactamases that confer resistance. In addition, many other strains of the *Enterobacteriaceae*, including *Enterobacter* spp.,

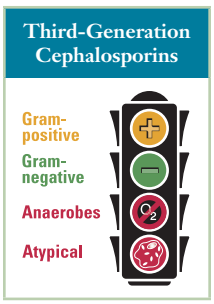


Table 5-12 Antimicrobial Activity of Third-Generation Cephalosporins

Gram-positive bacteria	*Streptococcus* pyogenes Viridans streptococci Many *Streptococcus pneumoniae* Modest activity against *Staphylococcus aureus*
Gram-negative bacteria	Some *Escherichia coli* Some *Klebsiella pneumoniae* *Proteus* spp. *Haemophilus influenzae* *Neisseria* spp. Some *Enterobacteriaceae*
Spirochetes	*Borrelia burgdorferi*

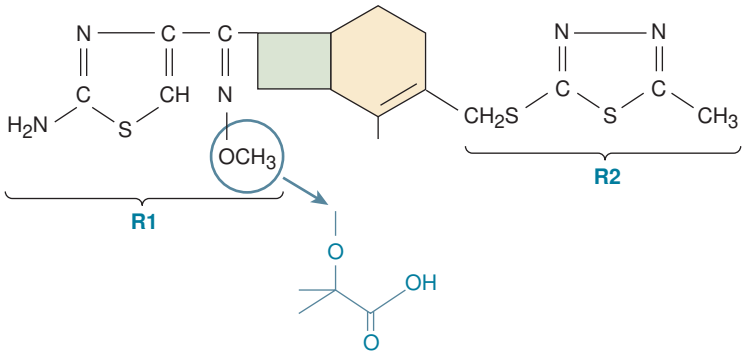


Figure 5-13. Structure of cefotaxime. The aminothiazolyl group at R1 is typical of many third-generation cephalosporins. In ceftazidime, the circled group is replaced by a α-hydroxyisobutyric acid group (shown in blue), which enhances activity against Pseudomonas aeruginosa.

Citrobacter freundii, *Providencia* spp., *Morganella morganii*, and *Serratia* spp., also initially show susceptibility to third-generation cephalosporins. However, these bacteria harbor chromosomally encoded inducible AmpC β-lactamases that may allow the emergence of resistance during treatment. Thus, it is now felt that infections caused by these organisms should either not be treated with third-generation cephalosporins or should be treated with these agents in conjunction with a second active agent, even if they appear to be susceptible by in vitro testing.

One shortcoming of most of the third-generation cephalosporins is their lack of activity against *P. aeruginosa*. To address this, the aminothiazolyl R1 side chain of ceftazidime was modified by the addition of an α-hydroxyisobutyric acid group (Fig. 5-13), which dramatically increases antipseudomonal activity. Unfortunately, this modification also results in decreased affinity for the PBPs of staphylococci. As a result, ceftazidime has enhanced activity against *P. aeruginosa* but limited activity against *S. aureus*.

Among the third-generation cephalosporins, ceftriaxone is notable for its long half-life. This agent is widely used because of the convenience of its once per day dosing.

FOURTH-GENERATION CEPHALOSPORINS

As mentioned earlier, the third-generation cephalosporins are powerful antimicrobial agents but suffer from susceptibility to the chromosomally encoded inducible AmpC β-lactamases of many of the *Enterobacteriaceae*. In addition, activity against *P. aeruginosa* is gained only at the expense of diminished antistaphylococcal activity. Attempts

PEARL

The *Enterobacteriaceae* is a large group of medically important gram-negative bacteria that includes the following genera: *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Morganella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia*.

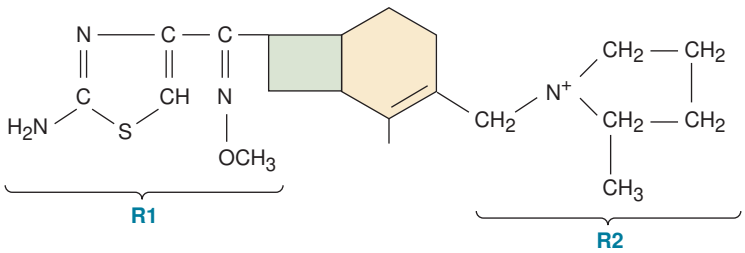


Figure 5-14. Structure of cefepime. The aminothiazolyl group typical of many third-generation cephalosporins is at R1, whereas a polar pyrrolidine group is at R2.

to address these deficiencies led to modifications of the R2 side chain of the third-generation cephalosporins while leaving the highly successful aminothiazolyl group at R1 unchanged (Fig. 5-14). The result of these efforts was the fourth-generation cephalosporin **cefepime**. The side chains of cefepime allow more rapid penetration through the outer membrane of many gram-negative bacteria, including *P. aeruginosa*. It also binds at a high affinity to many of the PBPs of these bacteria but is relatively resistant to hydrolysis by gram-negative β-lactamases, including the chromosomally encoded inducible AmpC β-lactamases of the *Enterobacteriaceae* (although the clinical relevance of this is controversial). These properties are attained without the loss of activity against aerobic gram-positive cocci. Thus, this incredibly powerful antibiotic has the best features of the various third-generation cephalosporins (antipseudomonal activity without loss of antistaphylococcal activity) and may also have enhanced activity against many of the *Enterobacteriaceae*. Cefepime has very limited anaerobic activity (Table 5-13).

FIFTH-GENERATION CEPHALOSPORINS

Ceftaroline is a new cephalosporin that has expanded activity against aerobic gram-positive cocci, causing some experts to refer to it as a fifth-generation agent. A 1,3-thiazole ring has been added to the R2 side chain of this cephalosporin, which confers upon it the ability to bind to the PBP of methicillin-resistant staphylococci (Fig. 5-15). As a result, ceftaroline has excellent activity against aerobic gram-positive

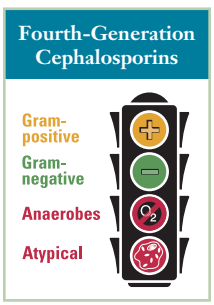


Table 5-13 Antimicrobial Activity of Fourth-Generation Cephalosporins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans streptococci Many *Streptococcus pneumoniae* Modest activity against *Staphylococcus aureus*
Gram-negative bacteria	Some *Escherichia coli* Some *Klebsiella pneumoniae* *Proteus* spp. *Haemophilus influenzae* *Neisseria* spp. Many other *Enterobacteriaceae* *Pseudomonas aeruginosa*

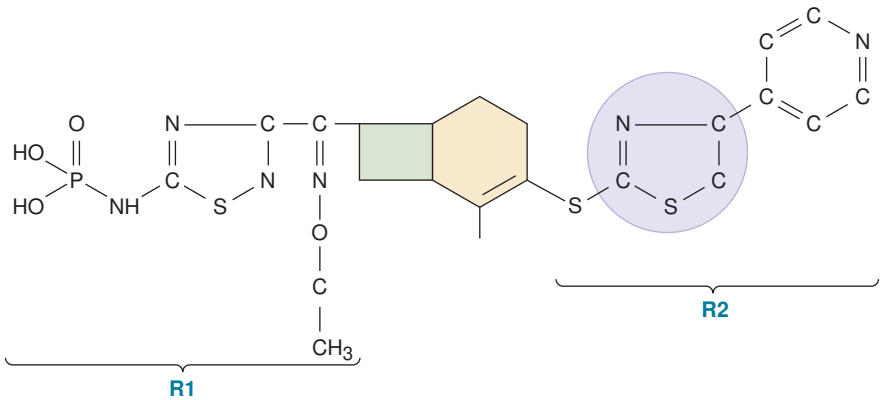


Figure 5-15. Structure of ceftaroline. The circled 1,3-thiazole ring in the R-2 side chain confers activity against methicillin-resistant *Staphylococcus aureus* strains.

cocci, including methicillin-resistant *S. aureus* and *S. epidermidis* and penicillin-resistant *S. pneumoniae* strains (Table 5-14). Its activities against aerobic gram-negative bacteria are similar to that of cefotaxime and ceftriaxone; it lacks antipseudomonal activity. Ceftaroline also has activity against anaerobic gram-positive bacteria but not against anaerobic gram-negative bacteria. This agent is administered as the inactive prodrug ceftaroline fosamil, which is rapidly converted to ceftaroline.

CEPHALOSPORIN/β-LACTAMASE INHIBITOR COMBINATIONS

Two recent additions to the cephalosporin family of antibiotics are **ceftazidime-avibactam** and **ceftolozane-tazobactam**.

Ceftazidime-avibactam broadens the spectrum of ceftazidime by combining it with the β-lactamase inhibitor avibactam. Unlike the β-lactamase inhibitors discussed up to this point, avibactam is not itself a β-lactam but does have structural features of β-lactams, which allows it to be bound by β-lactamases. The addition of avibactam to ceftazidime enhances the latter's activity against *Enterobacteriaceae*

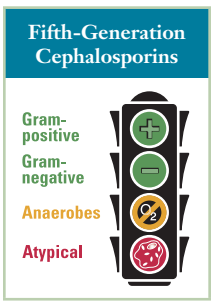


Table 5-14 Antimicrobial Activity of Fifth-Generation Cephalosporins

Gram-positive bacteria	*Streptococcus pyogenes* Viridans streptococci *Streptococcus pneumoniae* Staphylococci
Gram-negative bacteria	Some *Escherichia coli* Some *Klebsiella pneumoniae* *Proteus* spp. *Haemophilus influenzae* *Neisseria* spp. Some *Enterobacteriaceae*
Anaerobic bacteria	Some *Clostridium* spp.

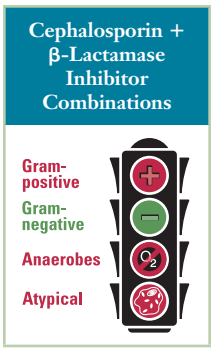


Table 5-15 Antimicrobial Activity of Cephalosporin + β-Lactamase Inhibitor Combinations

Gram-positive bacteria	*Streptococcus pyogenes* Viridans streptococci Many *Streptococcus pneumoniae*
Gram-negative bacteria	*Escherichia coli* *Klebsiella pneumoniae* *Proteus* spp. Other *Enterobacteriaceae* *Haemophilus influenzae* *Neisseria* spp. *Pseudomonas aeruginosa*

(including ceftazidime-resistant strains) and *P. aeruginosa* (Table 5-15). Arguably the most useful aspect of this antibiotic is its ability to inhibit the extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and *K. pneumoniae* carbapenemases (KPCs) (see Chapter 11 for a detailed description of these β-lactamases). The net result is enhanced activity against members of the *Enterobacteriaceae* and good activity against *P. aeruginosa*. This agent may be most useful in the treatment of infections caused by ESBL- and KPC-producing *Enterobacteriaceae*, for which few alternatives are currently available.

Whereas ceftazidime-avibactam combines an old cephalosporin with a novel β-lactamase inhibitor, ceftolozane-tazobactam combines an old β-lactamase inhibitor with a novel cephalosporin. Ceftolozane has features of ceftazidime, such as the

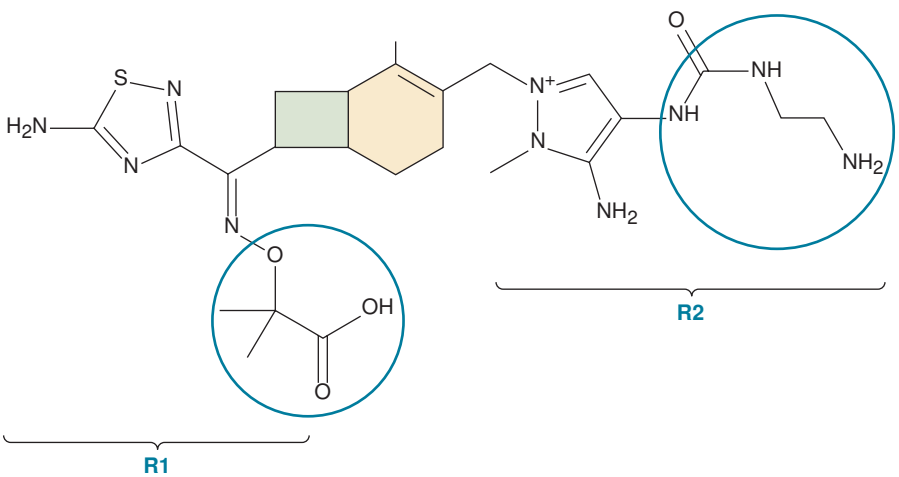


Figure 5-16. Structure of ceftolozane. The R1 side chain contains the α-hydroxyisobutyric acid group of ceftazidime (left circle), which enhances activity against *Pseudomonas aeruginosa*. However, the R2 group is bulkier than that of ceftazidime or other third-generation cephalosporins (right circle), which confers resistance to certain β-lactamases and further enhances antipseudomonal activity.

β-hydroxyisobutyric acid group on R1 but has a bulkier R2 side chain, which prevents cleavage by AmpC β-lactamases (compare Fig. 5-13 and Fig. 5-16). Together, these modifications confer enhanced activity against *P. aeruginosa* (Table 5-15). Tazobactam, which was described in the section on extended-spectrum penicillins with β-lactamase inhibitors, may provide activity against ESBL-producing *Enterobacteriaceae*, although this remains controversial.

TOXICITY

One of the attractions of the cephalosporins is their relatively favorable safety profile. Rarely, these agents cause immediate hypersensitivity reactions consisting of rash, urticaria, or anaphylaxis. In this regard, approximately 5% to 10% of individuals allergic to penicillin will also have a reaction to cephalosporins. Thus, it is usually recommended that individuals with a history of severe immediate hypersensitivity reactions to penicillin not be treated with cephalosporins. Other rare adverse effects include reversible neutropenia, thrombocytosis, hemolysis, diarrhea, and elevated liver function tests. Cefotetan may cause hypoprothrombinemia and, when used with alcohol, a disulfiram-like reaction. Both of these effects are associated with the methylthiotetrazole moiety at R2 of this agent (see Fig. 5-12). Because ceftriaxone is eliminated by biliary excretion, high doses of this agent may result in biliary sludging. Prolonged use of ceftaroline has been linked to neutropenia.

In summary, the cephalosporins vary markedly in their activities, but the following generalizations can be made: (1) First-generation agents have good activity against aerobic gram-positive bacteria. (2) Second-generation agents have modest activity against aerobic gram-positive, aerobic gram-negative, and (in some cases) anaerobic bacteria. (3) Third-generation agents have strong activity against aerobic gram-negative bacteria. (4) Fourth-generation agents have especially enhanced activity against aerobic gram-negative bacteria. (5) Fifth-generation agents have strong activity against aerobic gram-negative bacteria and excellent activity against aerobic gram-positive bacteria. (6) Cephalosporin/β-lactamase inhibitor combinations have enhanced activity against multidrug-resistant aerobic gram-negative bacteria.

HISTORY

Cephalosporins were discovered by the Italian scientist Giuseppe Brotzu in the 1940s. He noted that the seawater in the vicinity of a sewage outlet in Cagliari, Italy, periodically cleared, a phenomenon he suspected was due to the production of an inhibitory compound by a microbe growing in the water. He eventually identified the microbe as *Cephalosporium acremonium* and showed that it did indeed produce a substance that inhibited bacterial growth. This substance became the backbone from which early cephalosporins were synthesized. Interestingly, *Cephalosporium* fungi have been renamed *Acremonium* and occasionally cause infections in people.

Abraham EP. Cephalosporins 1945–1986. In: Williams JD, ed. *The Cephalosporin Antibiotics*. Auckland, New Zealand: Adis Press; 1987.

QUESTIONS

13. Cephalosporins are grouped into _____ and are all part of the larger class of antibiotics known as _____.

14. Like penicillins, cephalosporins act by binding _____, which are bacterial enzymes that function to assemble peptidoglycan.

15. First-generation cephalosporins are most useful in the treatment of infections caused by aerobic _____ bacteria.

16. Compared to first-generation agents, second-generation cephalosporins have enhanced activity against aerobic _____ bacteria. Some of these agents are also active against _____ bacteria.

17. Third-generation cephalosporins are most useful in the treatment of infections caused by aerobic _____ bacteria.

18. Compared to third-generation agents, fourth-generation cephalosporins have a broader spectrum of activity against aerobic gram-negative bacteria, including _____ and additional members of the _____.

19. Unlike other cephalosporins, fifth-generation cephalosporins have activity against _____ *S. aureus* strains.

20. Cephalosporin/β-lactamase inhibitor combinations are useful for treating multidrug-resistant aerobic _____ bacteria.

21. Use of high doses of _____ has been associated with biliary sludging.

22. Cephalosporins should be used with caution in individuals with severe immediate hypersensitivity reactions to _____.

ADDITIONAL READINGS

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Carbapenems

If β-lactams are viewed as a large extended family of antibiotics, then carbapenems are the arrogant young sons who drive a high-powered sports car and wear flashy clothes. These antibiotics are among the most broadly active antibiotics in use today. As such, they are often the last line of defense against many organisms that are resistant to other antimicrobial agents. Four members of this class, **imipenem**, **meropenem**, **doripenem**, and **ertapenem**, are commercially available (Table 5-16).

Table 5-16 The Carbapenems	
Parenteral Agents	**Oral Agents**
Imipenem/cilastatin	None
Meropenem	
Doripenem	
Ertapenem	

The structure of carbapenems is related to that of penicillins and cephalosporins (Fig. 5-17). A β-lactam ring is fused to a five-membered ring with variable side chains. The five-membered ring differs from the thiazolidine ring of penicillin in two ways (see circles in Fig. 5-17): A methylene group replaces sulfur, and the ring contains a double bond.

The structure of the carbapenems results in three properties that account for their incredibly broad spectra of activity. First, these molecules are quite small and have charge characteristics that allow them to utilize special porins in the outer membrane of gram-negative bacteria to gain access to the PBPs. Second, the structures of the carbapenems make them resistant to cleavage by most β-lactamases. Third, the carbapenems have an affinity for a broad range of PBPs from many different kinds of bacteria. As a result of these three properties, the carbapenems are adept at gaining access to the periplasm, resisting destruction by β-lactamases that reside there, and binding to PBPs to cause bacterial cell death.

Resistance to carbapenems occurs when bacteria overcome the advantageous aspects of these antibiotics. For example, *P. aeruginosa* is prone to develop resistance by acquiring mutations that result in loss of production of the outer membrane porin used by carbapenems to gain access to the periplasm. This often occurs together with overproduction of efflux pumps that limit accumulation of the drugs in the periplasmic space. *Enterococcus faecium* and methicillin-resistant staphylococci are resistant because they produce altered PBPs that do not bind these carbapenems. Finally, some bacteria have acquired the ability to produce extremely powerful β-lactamases that are capable of cleaving carbapenems.

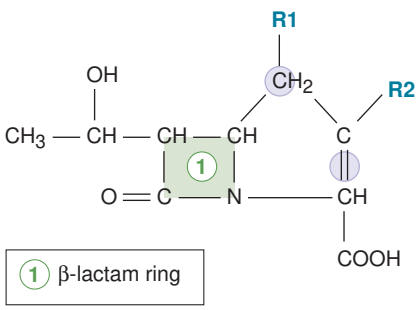

Figure 5-17. The structure of carbapenems. Circles indicate differences from the penicillin core structure.

HISTORY

That carbapenems, some of our most powerful antibiotics, are no longer active against some bacteria that were formerly susceptible, underscores the problem of emerging antimicrobial resistance. In 1946, Alexander Fleming warned against just such an eventuality. ". . . the public will demand [the drug and] . . . then will begin an era . . . of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted."

Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis.* 2013; 56:1445–1450.

IMIPENEM

Imipenem was the first commercially available carbapenem in the United States. Structurally, this compound differs from the other carbapenems in that it lacks an R1 side chain (Fig. 5-17). It is rapidly destroyed in the kidney by an enzyme called dehydropeptidase I. As a result, it is administered with cilastatin, an inhibitor of this enzyme.

Imipenem is active against many species of pathogenic bacteria (Table 5-17). Most streptococci, including many penicillin-resistant *S. pneumoniae* strains, are sensitive to this agent, as are many staphylococci (but not the "methicillin-resistant" staphylococci). Imipenem has truly remarkable activity against many different aerobic gram-negative bacteria, including *P. aeruginosa* and many of the highly resistant *Enterobacteriaceae*, such as *Enterobacter* and *Citrobacter* species. It also has excellent anaerobic coverage and is among the most useful agents in treating infections caused by these organisms. Like most antibiotics, however, it is not active against *C. difficile*.

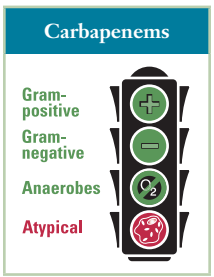

Table 5-17 Antimicrobial Activity of Carbapenems

Gram-positive bacteria	*Streptococcus pyogenes* Viridans group streptococci *Streptococcus pneumoniae* Modest activity against *Staphylococcus aureus* Some *enterococci* *Listeria monocytogenes*
Gram-negative bacteria	*Haemophilus influenzae* *Neisseria* spp. *Enterobacteriaceae* *Pseudomonas aeruginosa*
Anaerobic bacteria	*Bacteroides fragilis* Most other anaerobes

MEROPENEM

The structure of meropenem differs from that of imipenem at both the R1 and R2 side chains (Fig. 5-17). Importantly, whereas imipenem lacks an R1 side chain, meropenem has a methyl group at this position, which makes the molecule resistant to cleavage by the renal dehydropeptidase. As a result, meropenem does not need to be administered in conjunction with cilastatin.

Meropenem's spectrum of activity is essentially the same as imipenem. Thus, this agent also has excellent activity against aerobic gram-positive, aerobic gram-negative, and anaerobic bacteria.

DORIPENEM

Doripenem is a recently approved carbapenem. Like meropenem, it has a methyl group at R1 (see Fig. 5-17) and is not cleaved by renal dehydropeptidase. It differs from the other carbapenems at its R2 side chain but in general is similar to imipenem and meropenem in its spectrum of activity. Doripenem may not be as effective as imipenem in treating patients with ventilator-associated pneumonia.

ERTAPENEM

Ertapenem also has a methyl group at R1 (see Fig. 5-17) and therefore is not cleaved by renal dehydropeptidase. It differs from imipenem, meropenem, and doripenem at its R2 side chain, which accounts for its somewhat distinctive antimicrobial and pharmacologic properties; it is less active against aerobic gram-positive bacteria, *P. aeruginosa*, and *Acinetobacter* spp. than the other carbapenems. Ertapenem compensates for this weakness by requiring only once per day dosing.

TOXICITY

Carbapenem use is associated with several adverse events, including nausea and vomiting, diarrhea, rash, and drug fever. A more worrisome complication associated with carbapenems is seizures. Patients with preexisting central nervous system disease and with renal insufficiency are most at risk for this complication and should be given these drugs with caution. Initially, meropenem was felt to be less likely to cause seizures than imipenem, but this is now controversial. Results of animal experiments suggest that doripenem is less likely to cause seizures than the other carbapenems.

In summary, carbapenems have excellent activity against a broad spectrum of bacteria, including many aerobic gram-positive bacteria, most aerobic gram-negative

PEARL

Strains of *Enterococcus faecalis* that are susceptible to penicillin are also susceptible to carbapenems (except ertapenem). *Enterococcus faecium*, however, is resistant to all carbapenems.

Edwards JR. Meropenem: a microbiological overview. *J Antimicrob Chemother*. 1995;36(Suppl A):1–17.