INFECTIOUS DISEASES

A CLINICAL SHORT COURSE

THIRD EDITION

FREDERICK SOUTHWICK

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Infectious Diseases

A Clinical Short Course

Third Edition

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Infectious Diseases: A Clinical Short Course, Third Edition

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Infectious Diseases

A Clinical Short Course

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our Despite dire warnings that we are approaching the end of the antibiotic era, the incidence of antibiotic-resistant bacteria continues to rise. The proportions of penicillin-resistant Streptococcus pneumoniae, hospital-acquired methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant Enterococcus (VRE) strains continue to increase. Community-acquired MRSA (cMRSA) is now common throughout the world. Multiresistant Acinetobacter and Pseudomonas are everyday realities in many of our hospitals. The press is now warning the lay public of the existence of "dirty hospitals." As never before, it is critical that health care providers understand the principles of proper anti-infective therapy and use anti-infective agents judiciously. These agents need to be reserved for treatable infections–not used to calm the patient or the patient's family. Too often, patients with viral infections that do not warrant anti-infective therapy arrive at the physician's office expecting to be treated with an antibiotic. And health care workers too often prescribe antibiotics to fulfill those expectations. Physicians unschooled in the principles of microbiology utilize anti-infective agents just as they would more conventional medications, such as anti-inflammatory agents, anti-hypertensive medications, and cardiac drugs. They use one or two broad-spectrum antibiotics to treat all patients with.

Dedication

To my parents, Ann and Wayne Southwick, and children Ashley, Peter, Robyn, and Karli. And finally to my beautiful wife Kathie Southwick for her loving encouragement and continual support.

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Preface

The challenges of infectious diseases are daunting. As our world shrinks, person-to-person spread of influenza and coronavirus has the potential to cause pandemics. The overuse of antibiotics continues to increase the prevalence of highly resistance bacteria. Increasing numbers of patients receive prosthetic devices that subsequently become infected. New immunosuppressive treatments of patients with connective tissue diseases and inflammatory bowel disease increase the risk of opportunistic infections. HIV remains with us and thanks to multiple antiretroviral medications, these patients are experiencing nearly normal life spans increasing the number of HIV-infected patients requiring continued care.

How do medical students, physician assistants, nurse practitioners, and physicians learn this important subspecialty? The textbooks on infectious diseases are generally over 1000 pages in length. However, the average clinician does not have time to read these books in their entirety. There are Internet products that offer detailed descriptions of each individual infectious disease. However, these products offer a fragmented approach that makes a full understanding of the field difficult. *Infectious Diseases: A Clinical Short Course* concisely covers the key areas of infectious diseases and is designed to be read in 30 days, the usual duration of a clinical elective. At the beginning of each chapter, the estimated time required to read each chapter is included to allow readers to budget their time. To stimulate the reader's attention, each chapter begins with a series of guiding questions. These questions are followed by an estimate of the potential severity of each disease to provide the less experienced clinician with a sense of how quickly he or she should be initiating treatment. Actual clinical cases are included for every major disease to link the facts to real patients. Key points are summarized in text boxes to reinforce the most important facts, and allow the reader to quickly review each topic. This tool is particularly effective for reviewing board examinations.

The third edition has included antibiograms for each major antibiotic class to provide a visual depiction of the spectrum of each individual antibiotic, and allow the busy clinician to quickly pick the most appropriate antibiotic to cover the pathogens identified on culture. A table listing the most commonly used outpatient antibiotics and their dosing has been added. The chapter (Chapter 2) on sepsis has been completely rewritten now emphasizing how to recognize sepsis in its earliest stages when treatment can be lifesaving. In Chapter 3, The Febrile Patient, a greater emphasis has been made on the diagnostic approach to fever on the wards and in the intensive care unit (ICU). Chapter 4, Pulmonary Infections, has been updated and now emphasizes the use of simple objective criteria to decide on hospitalization and ICU triage. In Chapter 5, new guidelines for the diagnosis and management of sinusitis are included. In Chapter 6, the latest studies on the use of glucocorticoids for meningitis are reviewed, and in Chapter 7, the latest guidelines for the treatment of endocarditis have been included. Chapter 8 outlines the most up-to-date treatments of infectious diarrhea as well as hepatitis B and C. Chapter 9 has been updated to reflect the latest CDC guidelines for the treatment of sexually transmitted diseases. Chapter 10 has added the latest epidemiologic and treatment approaches for methicillin-resistant *Staphylococcus aureus* (MRSA) soft tissue infections, and Chapter 11 includes the latest consensus on how to manage prosthetic joint infections. Chapter 12 continues to provide a succinct up-to-date review of the major parasitic infections. Chapter 13, Emerging Pathogens, is an exciting new chapter that provides a new perspective on zoonotic infections, and also covers the potential bacterial bioterrorist agents. Chapter 14 reviews the latest data on influenza virus including

H1N1 and avian influenza. Chapter 15 provides a step-by-step approach to the management of immunocompromised patients, which is based on the very latest clinical research. Finally, Chapter 16 has been updated to reflect the latest advances in the treatment of HIV.

The third edition emphasizes the use of the Infectious Diseases Society of America (IDSA) guidelines to assure that the management of each infectious disease is consistent throughout the country and the world. Patients will come to expect that all clinicians apply the best practices that are based on current clinical data and the recommendations of the experts in the field. *Infectious Diseases: A Clinical Short Course* distills these guidelines into helpful tables that will allow the busy clinician to accomplish this important goal.

Acknowledgments

I want to thank Morton Swartz, the former Chief of Infectious Diseases at the Massachusetts General Hospital, for inspiring my love of infectious diseases. I also want to thank Drs. James McGuigan, the former Chairman of the Department of Medicine at the University of Florida, and Tom Stossel, Professor of Medicine at the Harvard Medical School, who have patiently mentored me throughout my career. I appreciate the excellent and timely contributions by my colleagues and friends, Drs. Daniel Lew, Sankar Swaminathan, and Bernard Hirschel. Finally, I want to thank James Shanahan of McGraw-Hill for his patient guidance and encouragement during the writing of all three editions.

Infectious Diseases

A Clinical Short Course

Contents

Anti-Infective Therapy

1

Time Recommended to Complete: 3 days

Frederick S. Southwick, M.D.

GUIDING QUESTIONS

1. *Are we at the end of the antibiotic era?*
2. *Why are "superbugs" suddenly appearing in our hospitals?*
3. *How do bacteria become resistant to antibiotics?*
4. *How can the continued selection of highly resistant organisms be prevented?*
5. *Is antibiotic treatment always the wisest course of action?*
6. *Does one antibiotic cure all infections?*
7. *What are the strategies that underlie optimal antibiotic usage?*
8. *How is colonization distinguished from infection, and why is this distinction important?*

Despite dire warnings in the 1990s that we were approaching the end of the antibiotic era, the incidence of antibiotic-resistant bacteria continues to rise. The proportions of penicillin-resistant *Streptococcus pneumoniae*, hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* (VRE) strains continue to steadily increase in many hospitals. Community-acquired MRSA (cMRSA) has spread throughout the world. Multiresistant *Acinetobacter* and *Pseudomonas* are everyday realities in most of our hospitals. In the past, we could depend on the pharmaceutical industry to develop new anti-infective agents to overcome these highly resistant bacteria. However, these companies are no longer investing in the development of anti-infective medications because of the high cost of development and limited profits. As never before, it is critical that health care providers understand the principles of proper anti-infective therapy and use anti-infective agents judiciously. These agents need to be reserved for treatable infections—not used to calm the patient or the patient's family. Too often caregivers treat patients with antibiotics at the first sign of fever, and despite evidence suggesting a viral infection and negative bacterial cultures they continue this treatment for prolonged periods.

Physicians unschooled in the principles of microbiology utilize anti-infective agents just as they would more conventional medications, such as anti-inflammatory agents, antihypertensive medications, and cardiac drugs. They use one or two broad-spectrum antibiotics to treat all patients with suspected infections, and fail to consult an expert in infectious disease or utilize well-established guidelines to assist in the proper management of anti-infective therapy.

Many excellent broad-spectrum antibiotics can effectively treat most bacterial infections without requiring a specific causative diagnosis. However, overuse of empiric broad-spectrum antibiotics has resulted in the selection of highly resistant pathogens. A simplistic approach to anti-infective therapy and establishment of a fixed series of simple rules concerning the use of these agents is unwise and has proved harmful to patients. Such an approach ignores the remarkable adaptability of bacteria, fungi, and viruses. It is no coincidence that these more primitive life forms have survived for millions of years, far longer than the human race.

The rules for the use of anti-infective therapy are dynamic and must take into account the ability of these pathogens to adapt to the selective pressures exerted by the overuse of antibiotic, antifungal, and antiviral agents. The days of the "shotgun" approach to infectious diseases must end, or more and more patients will become infected with multiresistant organisms that cannot be treated. Many hospitals are turning to antibiotic stewardship programs that limit the access to costly broad-spectrum antibiotics. Only through the judicious use of anti-infective therapy combined with infection control measures we can hope to slow the arrival of the end of the antibiotic era.

KEY POINTS

About Anti-Infective Therapy

1. Too often, antibiotics are prescribed to fulfill the patient's expectations, rather than to treat a true bacterial infection.
2. A single antibiotic cannot meet all infectious disease needs.
3. Physicians ignore the remarkable adaptability of bacteria, fungi, and viruses at their patient's peril.
4. Anti-infective therapy is dynamic and requires a basic understanding of microbiology.
5. The "shotgun" approach to infectious diseases must end, or we may truly experience the end of the antibiotic era.

ANTIBIOTIC RESISTANCE

GENETIC MODIFICATIONS LEADING TO ANTIMICROBIAL RESISTANCE

To understand why antibiotics must be used judiciously, the physician needs to understand how bacteria are able to adapt to their environment. Point mutations can develop in the DNA of bacteria as they replicate. These mutations occur in the natural environment, but are of no survival advantage unless the bacteria are placed under selective pressures. In the case of a mutation that renders a bacterium resistant to a specific antibiotic, exposure to the specific antibiotic allows the bacterial clone that possesses the antibiotic resistance mutation to grow, while bacteria without the mutation die and no longer compete for nutrients. Thus, the resistant strain becomes the dominant bacterial flora. In addition to point mutations, bacteria can also use three major mechanisms to transfer genetic material among themselves:

1. **Conjugation.** Bacteria often contain circular, double-stranded DNA structures called plasmids. These circular DNA structures lie outside the bacterial genome (Figure 1.1). Plasmids often carry resistance ("R") genes. Through a mechanism called "conjugation," plasmids can be transferred from one bacterium to another. The plasmid encodes for the formation of a pilus on the donor bacteria's outer surface. The pilus attaches to a second bacterium and serves as bridge for the transfer of the plasmid DNA from the donor to the recipient bacterium. Using this mechanism, a single resistant bacterium can transfer resistance to other bacteria.
2. **Transduction.** Bacteriophages are protein-coated DNA segments that attach to the bacterial wall and inject DNA in a process called "transduction." These infective particles can readily transfer resistance genes to multiple bacteria.
3. **Transformation.** Donor bacteria can also release linear segments of chromosomal DNA, which is then taken up by recipient bacteria and incorporated into the recipient's genome. This process is called "transformation," and the naked DNA capable of incorporating into the genome of recipient bacteria is called a transposon (Figure 1.1). Natural transformation most commonly occurs in *Streptococcus*, *Haemophilus*, and *Neisseria* species. Transposons can transfer multiple antibiotic resistance genes in a single event and have been shown to be responsible for high-level vancomycin resistance in enterococci.

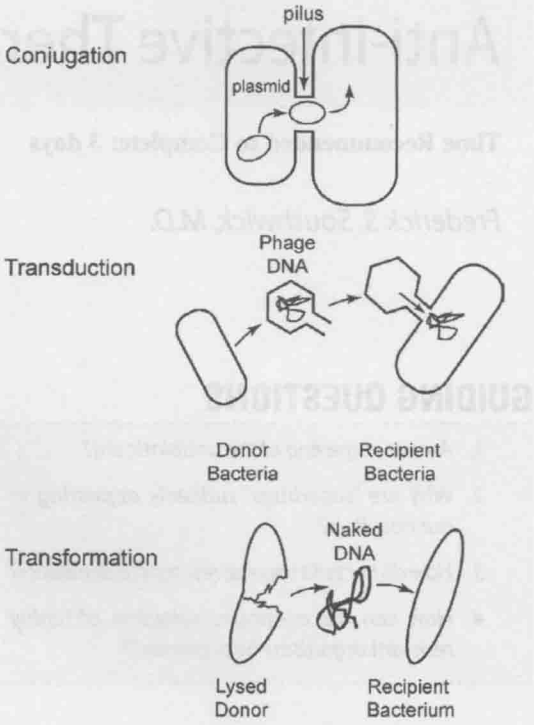

Figure 1.1. Mechanisms by which bacteria transfer antibiotic resistance genes.

Thus, bacteria possess multiple ways to transfer their DNA, and they promiscuously share genetic information.

KEY POINTS

About Antibiotic Resistance

1. Bacteria can quickly alter their genetic makeup by
   a) point mutation.
   b) transfer of DNA by plasmid conjugation.
   c) transfer of DNA by bacteriophage transduction.
   d) transfer of naked DNA by transposon transformation.
2. The ability of bacteria to share DNA provides a survival advantage, allowing them to quickly adapt to antibiotic exposure.
3. Biochemical alterations leading to antibiotic resistance include
   a) degradation or modification of the antibiotic.
   b) reduction in the bacterial antibiotic concentration by inhibiting entry or by efflux pumps.
   c) modification of the antibiotic target.
4. Under the selection pressure of antibiotics, the question is not *whether*, but *when* resistant bacteria will take over.

Virtually any part of a bacterium's genome can be transferred, and this promiscuity provides a survival advantage, allowing bacteria to quickly adapt to their environment.

BIOCHEMICAL MECHANISMS FOR ANTIMICROBIAL RESISTANCE

What are some of the proteins that these resistant genes encode for, and how do they work?

The mechanisms by which bacteria resist antibiotics can be classified into three major groups:

- Degradation or modification of the antibiotic
- Reduction in the bacterial antibiotic concentration
- Modification of the antibiotic target

Degradation or Modification of the Antibiotic

β-Lactamases

Many bacteria synthesize one or more enzymes called β-lactamases that inactivate antibiotics by breaking the amide bond on the β-lactam ring. Transfer of β-lactamase activity occurs primarily through plasmids and transposons.

Twenty-four classes of β-lactamases and over 900 individual enzymes have been described. Some preferentially break down penicillins (e.g., TEM-1 in *Escherichia coli*, and SHV-1 for *Klebsiella*); others preferentially destroy specific cephalosporins or carbenicillin. Extended-spectrum β-lactamases (ESBL, example: SHV-2) readily destroy most cephalosporins, but are susceptible to β-lactamase inhibitors such as clavulanate. Another class of β-lactamase is resistant to clavulanate (CTX-M family). Some bacteria are able to produce β-lactamases called carbapenemases that inactivate the carbapenems (e.g., *Klebsiella*-producing carbapenemase, KPC, Oxa-type enzymes produced by *Acinetobacter*).

Gram-negative bacilli produce a broader spectrum of β-lactamases than do gram-positive organisms, and therefore infections with gram-negative organisms more commonly arise in patients treated for prolonged periods with broad-spectrum antibiotics. In some instances, β-lactamase activity is low before the bacterium is exposed to antibiotics; however, following exposure, β-lactamase activity is induced. *Enterobacter* is a prime example. This gram-negative bacterium may appear sensitive to cephalosporins on initial testing. Following cephalosporin treatment, β-lactamase activity increases, resistance develops, and the patient's infection relapses. For this reason, third-generation cephalosporins are not recommended for serious *Enterobacter* infections.

Other Enzyme Modifications of Antibiotics

Erythromycin is readily inactivated by an esterase that hydrolyzes the lactone ring of the antibiotic. This esterase has been identified in *E. coli*. Other plasmid-mediated erythromycin inactivating enzymes have been discovered in *Streptococcus* species and *S. aureus*. Chloramphenicol is inactivated by chloramphenicol acetyltransferase, which has been isolated from both gram-positive and gram-negative bacteria. Similarly, aminoglycosides can be inactivated by acetyltransferases. Bacteria also inactivate this class of antibiotics by phosphorylation and adenylation.

These resistance enzymes are found in many gram-negative strains and are increasingly detected in enterococci, *S. aureus* and *S. epidermidis*.

Reduction in the Bacterial Antibiotic Concentration

Interference with Antibiotic Entry

For an antibiotic to work, it must be able to penetrate the bacterium and reach its biochemical target. Gram-negative bacteria contain an outer lipid coat that impedes penetration by hydrophobic reagents (such as most antibiotics). The passage of hydrophobic antibiotics is facilitated by the presence of porins—small channels in the cell walls of gram-negative bacteria that allow the passage of charged molecules. Mutations leading to the loss of porins can reduce antibiotic penetration and lead to antibiotic resistance. Following prolonged exposure to

vancomycin, MRSA can develop a thickened cell wall requiring higher vancomycin concentrations to inhibit bacterial growth (vancomycin intermediate *S. aureus*, VISA).

Production of Efflux Pumps

Transposons have been found that encode for an energy-dependent pump that can actively pump tetracycline out of bacteria. Active efflux of antibiotics has been observed in many enteric gram-negative bacteria, and this mechanism is used to resist tetracycline, macrolide, aminoglycosides, and fluoroquinolone antibiotic treatment (e.g., MexXY). *S. aureus*, *S. epidermidis*, *S. pyogenes*, group B streptococci, and *S. pneumoniae* also can utilize energy-dependent efflux pumps to resist antibiotics.

Modification of the Antibiotic Target

Alterations of Cell Wall Precursors

Alteration of cell wall precursors is the basis for VRE. Vancomycin and teicoplanin binding requires that D-alanine-D-alanine be at the end of the peptidoglycan cell wall precursors of gram-positive bacteria. Resistant strains are found predominantly in *Enterococcus faecium* and less commonly in *Enterococcus faecalis* contain the vanA or vanB transposon that encodes a protein that synthesizes D-alanine-D-lactate instead of D-alanine-D-alanine at the end of the peptidoglycan precursor. Loss of the terminal D-alanine markedly reduces vancomycin and teicoplanin binding, allowing the mutant bacterium to survive and grow in the presence of these antibiotics. Fortunately, the transfer of these transposons to *S. aureus* is exceedingly rare.

Changes in Target Enzymes

Penicillins and cephalosporins bind to specific proteins called penicillin-binding proteins (PBPs) in the bacterial cell wall. Penicillin-resistant *S. pneumoniae* demonstrate decreased numbers of PBPs or PBPs that bind penicillin with lower affinity, or both. Decreased penicillin binding reduces the ability of the antibiotic to kill the targeted bacteria.

The basis for antibiotic resistance in MRSA is production of a low-affinity PBP encoded by the *mecA* gene. Mutations in the target enzymes dihydropteroate synthetase and dihydrofolate reductase respectively cause sulfonamide and trimethoprim resistance. Single amino-acid mutations that alter DNA gyrase function can result in resistance to fluoroquinolones.

Alterations in Ribosomal Binding Site

Tetracyclines, macrolides, lincosamides, and aminoglycosides all act by binding to and disrupting the function of bacterial ribosomes (see the descriptions of individual antibiotics later in this chapter). A number of resistance genes encode for enzymes that demethylate adenine residues on bacterial ribosomal RNA, inhibiting antibiotic binding to the ribosome. Ribosomal resistance to gentamicin, tobramycin, and amikacin is less common because these aminoglycosides have several binding sites on the bacterial ribosome and require multiple bacterial mutations before their binding is blocked.

CONCLUSIONS

Bacteria can readily transfer antibiotic-resistance genes. Bacteria have multiple mechanisms to destroy antibiotics, lower the antibiotic concentration, and interfere with antibiotic binding. Under the selective pressures of prolonged antibiotic treatment, the question is not *whether*, but *when* resistant bacteria will take over.

ANTI-INFECTIVE AGENT DOSING

The characteristics that need to be considered when administering antibiotics include absorption (when dealing with oral antibiotics), volume of distribution, metabolism, and excretion. These factors determine the dose of each drug and the time interval of administration. To effectively clear a bacterial infection, depending on the class of antibiotics, serum levels of the antibiotic need to be maintained above the *minimum inhibitory concentration (MIC)* for a significant period. For each pathogen, the MIC is determined by serially diluting the antibiotic into liquid medium containing 10^4 bacteria per milliliter. Inoculated tubes are incubated overnight until broth without added antibiotic has become cloudy or turbid as a result of bacterial growth. The lowest concentration of antibiotic that prevents active bacterial growth—that is, the liquid media remains clear—constitutes the MIC (Figure 1.2). Automated analyzers can now quickly determine, for individual pathogens, the MICs for multiple antibiotics, and these data serve to guide the physician's choice of antibiotics.

Clinical laboratories utilize MIC combined with studies examining achievable antibiotic levels (pharmacokinetics and pharmacodynamics, see below) in humans to determine whether an organism is *sensitive, intermediate, or resistant* to a specific antibiotic. This value is called the *breakpoint* or cutoff, and is the concentration (MIC) above which there is a high likelihood of treatment success, and below which there is considerable risk of failure. At the present time, different countries and different organizations utilize different criteria to determine breakpoints, and experts strongly recommend the acceptance of an international standard for calculating breakpoints.

The mean bactericidal concentration (MBC) is determined by taking each clear tube and inoculating a

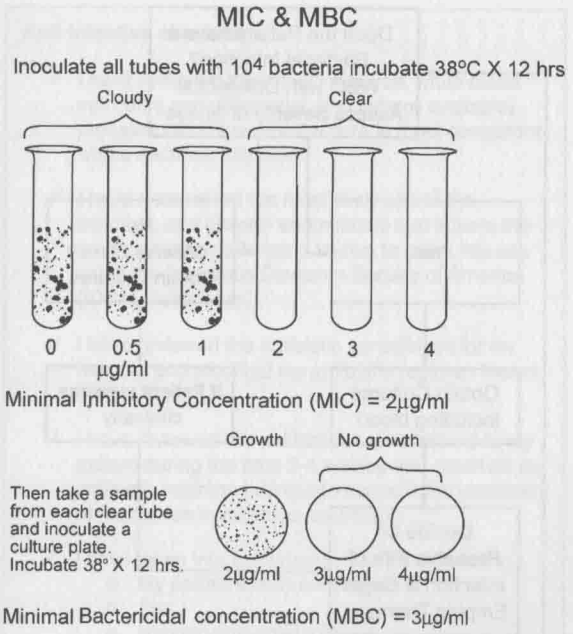

Figure 1.2. Understanding the minimum inhibitory concentration and the minimal bactericidal concentration.

plate of solid medium with the solution. Plates are then incubated to allow colonies to form. The lowest concentration of antibiotic that blocks all growth of bacteria—that is, no colonies on solid medium—represents the MBC. Because this method is technically cumbersome, this value is now rarely determined.

Successful cure of an infection depends on multiple host factors in addition to serum antibiotic concentration. However, investigators have attempted to predict successful treatment by plotting serum antibiotic levels against time. Two parameters have found to correlate with cure in both animal and human studies (Figure 1.3): *time above the MIC (T>MIC)*, and the ratio of the *area under the curve (AUC)* to the MIC (*AUC/MIC*).

Cure rates for β-lactam antibiotics are maximized by maintaining serum levels above the MIC for >50% of the time. Peak antibiotic concentrations are of less importance for these antibiotics, and serum concentrations above eight times the MIC are of no benefit other than to enhance penetration into less permeable body sites.

Unlike β-lactam antibiotics, aminoglycosides and fluoroquinolones demonstrate concentration-dependent killing. In vitro studies show that these antibiotics demonstrate greater killing the higher their concentrations exceed the MIC. High peak levels of these antibiotics are more effective than low peak levels at curing infections. Therefore, for treatment with aminoglycosides and fluoroquinolones AUC/MIC is most helpful for

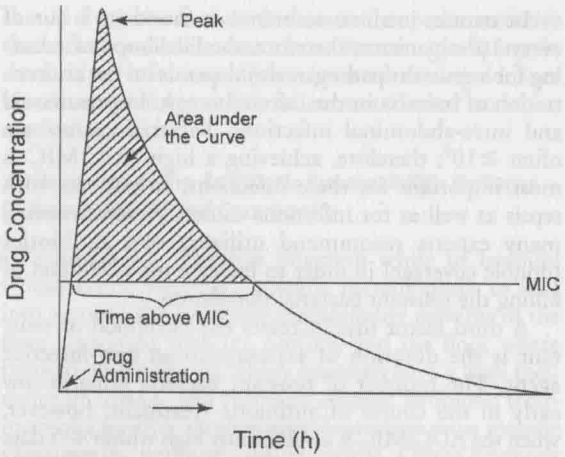

Figure 1.3. Pharmacokinetics of a typical antibiotic.

maximizing effectiveness. For fluoroquinolones, best outcomes in community-acquired pneumonia may be achieved when the AUC/MIC is >34.

Maintenance of a high AUC/MIC has recently been shown to be a critical factor for preventing the development of antibiotic resistance particularly in *Pseudomonas aeruginosa* and other nonfermenting gram-negative bacteria (*Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*). For *P. aeruginosa*, an AUC/MIC of approximately 200 is required. To prevent the development of fluoroquinolone resistance to *S. pneumoniae*, in vitro studies have suggested that AUC/MIC should be >50.

KEY POINTS

About Antibiotic Dosing

1. Absorption, volume of distribution, metabolism, and excretion all affect serum antibiotic levels.
2. Mean inhibitory concentration (MIC) is helpful in guiding antibiotic choice.
3. To maximize success with β-lactam antibiotics, serum antibiotic levels should be above the MIC for at least 50% of the time (T > MIC > 50%).
4. To maximize success with aminoglycosides and fluoroquinolones, high-peak concentration and high AUC/MIC ratio are recommended.
5. Development of resistance can be prevented by
   a) administering sufficiently high doses of antibiotics to achieve very high AUC/MIC ratios, 50–200 depending on the organism.
   b) short courses of antibiotic, ideally 5 days or less.