Antimicrobial drugs exploit differences in structure or biochemical function between host and parasite. Modern chemotherapy is traced to Paul Ehrlich, a pupil of Robert Koch, who devoted his career to discovering agents that possessed selective toxicity so that they might act as so-called “magic bullets” in the fight against infectious diseases. The remarkable efficacy of modern antimicrobial drugs still retains a sense of the miraculous. Sulfonamides, the first clinically successful broad-spectrum antibacterial agents, were produced in Germany in 1935.

However, it was the discovery of the antibiotic penicillin, a fungal metabolite, by Fleming in 1929, and its subsequent development by Chain and Florey during World War II, that led to the antibiotic revolution. Within a few years of the introduction of penicillin, many other antibiotics were described. This was followed by the development of semisynthetic and synthetic (e.g., sulfonamides and fluoroquinolones) antimicrobial agents, which has resulted in an increasingly powerful and effective array of compounds used to treat infectious diseases. In relation to this, the term antibiotic has been defined as a low molecular weight substance produced by a microorganism that at low concentrations inhibits or kills other microorganisms. In contrast, the word antimicrobial has a broader definition than antibiotic and includes any substance of natural, semisynthetic, or synthetic origin that kills or inhibits the growth of a microorganism but causes little or no damage to the host. In many instances, antimicrobial agent is used synonymously with antibiotic.

The marked structural and biochemical differences between prokaryotic and eukaryotic cells give antimicrobial agents greater opportunities for selective toxicity against bacteria than against other microorganisms such as fungi, which are nucleated like mammalian cells, or viruses, which require their host’s genetic material for replication. Nevertheless, in recent years increasingly effective antifungal and antiviral drugs have been introduced into clinical practice.

Important milestones in the development of antibacterial drugs are shown in Figure 1.1. The therapeutic use of these agents in veterinary medicine has usually followed their use in human medicine because of the enormous costs of development. However, some antibacterial drugs have been developed specifically for animal health and production (e.g., tylosin, tiamulin, tilmicosin, ceftiofur, tulathromycin, gamithromycin, tildipirosin). Figure 1.1 highlights the relationship between antibiotic use and the development of resistance in many target microorganisms.

Spectrum of Activity of Antimicrobial Drugs

Antimicrobial drugs may be classified in a variety of ways, based on four basic features.

Class of Microorganism

Antiviral and antifungal drugs generally are active only against viruses and fungi, respectively. However, some imidazole antifungal agents have activity against staphylococci...
Figure 1.1. Milestones in human infectious disease and their relationship to development of antibacterial drugs. Modified and reproduced with permission from Kammer, 1982.
and nocardioform bacteria. Antibacterial agents are described as narrow-spectrum if they inhibit only bacteria or broad-spectrum if they also inhibit mycoplasma, rickettsia, and chlamydia. The spectrum of activity of common antibacterial agents is shown in Table 1.1.

### Table 1.1. Spectrum of activity of common antibacterial drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class of Microorganism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteria</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>+</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>+</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>+</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>+</td>
</tr>
<tr>
<td>Glycopyclines</td>
<td>+</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>+</td>
</tr>
<tr>
<td>Macrolides</td>
<td>+</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>+</td>
</tr>
<tr>
<td>Pleuromutins</td>
<td>+</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>+</td>
</tr>
<tr>
<td>Streptogamins</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>+</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>+</td>
</tr>
</tbody>
</table>

+/-: Activity against some protozoa.

### Antibacterial Activity

Some antibacterial drugs are also considered narrow-spectrum in that they inhibit only Gram-positive or Gram-negative bacteria, whereas broad-spectrum drugs inhibit both Gram-positive and Gram-negative bacteria. However, this distinction is not always absolute, as some agents may be primarily active against Gram-positive bacteria but will also inhibit some Gram-negatives (Table 1.2).

### Bacteriostatic or Bactericidal Activity

The minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent required to prevent the growth of the pathogen. In contrast, the minimum bactericidal concentration (MBC) is the lowest concentration of an antimicrobial agent required to kill the pathogen. Antimicrobials are usually regarded as bactericidal if the MBC is no more than 4 times the MIC. Under certain clinical conditions this distinction is important, but it is not absolute. In other words, some drugs are often bactericidal (e.g., beta-lactams, aminoglycosides) and others are usually bacteriostatic (e.g., chloramphenicol, tetracyclines), but this distinction is an approximation, depending on both the drug concentration at the site of infection and the microorganism involved. For example, benzyl penicillin is bactericidal at usual therapeutic concentrations and bacteriostatic at low concentrations.

### Time- or Concentration-Dependent Activity

Antimicrobial agents are often classified as exerting either time-dependent or concentration-dependent activity depending on their pharmacodynamic properties. The pharmacodynamic properties of a drug address the relationship between drug concentration and antimicrobial activity (chapter 5). Drug pharmacokinetic features, such as serum concentrations over time and area under the serum concentration-time curve (AUC), when integrated with MIC values, can predict the probability of bacterial eradication and clinical success. These pharmacokinetic and pharmacodynamic relationships are also important in preventing the selection and spread of resistant strains. The most significant factor determining the efficacy of beta-lactams, some macrolides, tetracyclines, trimethoprim-sulfonamide combinations, and chloramphenicol is the length of time that serum concentrations
exceed the MIC of a given pathogen. Increasing the concentration of the drug several-fold above the MIC does not significantly increase the rate of microbial killing. Rather, it is the length of time that bacteria are exposed to concentrations of these drugs above the MIC that dictates their rate of killing. Optimal dosing of such antimicrobial agents involves frequent administration. Other antimicrobial agents such as the aminoglycosides, fluoroquinolones, and metronidazole exert concentration-dependent killing characteristics. Their rate of killing increases as the drug concentration increases above the MIC for the pathogen and it is not necessary or even beneficial to maintain drug levels above the MIC between doses. Thus, optimal dosing of aminoglycosides and fluoroquinolones involves administration of high doses at long dosing intervals. Some drugs exert characteristics of both time- and concentration-dependent activity. The best predictor of efficacy for these drugs is the 24-hour area under the serum concentration versus time curve (AUC)/MIC ratio. Glycopeptides, rifampin, and, to some extent, fluoroquinolones fall within this category (chapter 5).

### Mechanisms of Action of Antimicrobial Drugs

#### Antibacterial Drugs

Figure 1.2 summarizes the diverse sites of action of the antibacterial drugs. Their mechanisms of action fall into four categories: inhibition of cell wall synthesis, damage to cell membrane function, inhibition of nucleic acid synthesis or function, and inhibition of protein synthesis.

Antibacterial drugs that affect cell wall synthesis (beta-lactam antibiotics, bacitracin, glycopeptides) or
inhibit protein synthesis (aminoglycosides, chloramphenicol, lincosamides, glycyclines, macrolides, oxazolidinones, streptogramins, pleuromutilins, tetracyclines) are more numerous than those that affect cell membrane function (polymyxins) or nucleic acid function (fluoroquinolones, nitroimidazoles, nitrofurans, rifampin), although the development of fluoroquinolones has been a major advance in antimicrobial
therapy. Agents that affect intermediate metabolism (sulfonamides, trimethoprim) have greater selective toxicity than those that affect nucleic acid synthesis.

**Searching for New Antibacterial Drugs**

Infection caused by antibiotic-resistant bacteria has been an increasingly growing concern in the last decade. The speed with which some bacteria develop resistance considerably outpaces the slow development of new antimicrobial drugs. Since 1980, the number of antimicrobial agents approved for use in people in the United States has fallen steadily (Figure 1.3). Several factors such as complex regulatory requirements, challenges in drug discovery, and the high cost of drug development coupled with the low rate of return on investment antibiotics provide compared with drugs for the treatment of chronic conditions all contribute to driving pharmaceutical companies out of the antimicrobial drug market. This has left limited treatment options for infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci. The picture is even bleaker for infections cause by some Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum beta-lactamase (ESBL)-resistant *E. coli*, *Klebsiella* spp., and *Enterobacter* spp., which are occasionally resistant to all the antimicrobial agents on the market. Judicious use of the antibiotics currently available and better infection control practices might help prolong the effectiveness of the drugs that are currently available. However, even if we improve these practices, resistant bacteria will continue to develop and new drugs will be needed.

The approaches in the search for novel antibiotics include further development of analogs of existing agents; identifying novel targets based on a biotechnological approach, including use of information obtained from bacterial genome sequencing and gene cloning; screening of natural products from plants and microorganisms from unusual ecological niches other than soil; development of antibacterial peptide molecules derived from phagocytic cells of many species; screening for novel antimicrobials using combinatorial chemical libraries; development of synthetic antibacterial drugs with novel activities, such as oxazolidinones; development of new antibiotic classes that were abandoned early in the antibiotic revolution because there were existing drug classes with similar activities; development of “chimeramycins” by laboratory recombination of genes encoding antibiotics of different classes; and combination of antibacterial drugs with iron-binding chemicals targeting bacterial iron uptake mechanisms.

**Antifungal Drugs**

Most currently used systemic antifungal drugs damage cell membrane function by binding ergosterols that are unique to the fungal cell membrane (polyenes, azoles; chapter 20). The increase in the number of

![Figure 1.3](image-url)  
**Figure 1.3.** New antimicrobial agents approved for use in people in the United States since 1980.
HIV-infected individuals and of people undergoing organ or bone marrow transplants has resulted in increased numbers of immunosuppressed individuals in many societies. The susceptibility of these people to fungal infections has renewed interest in the discovery and development of new antifungal agents. The focus of antifungal drug development has shifted to cell wall structures unique to fungi (1,3-β-D-glucan synthase inhibitors, chitin synthase inhibitors, mannoprotein binders; Figure 20.1).

Antibacterial Drug Interactions: Synergism, Antagonism, and Indifference

Knowledge of the different mechanisms of action of antimicrobials provides some ability to predict their interaction when they are used in combination. It was clear from the early days of their use that combinations of antibacterials might give antagonistic rather than additive or synergistic effects. Concerns regarding combinations include the difficulty in defining synergism and antagonism, particularly their method of determination in vitro; the difficulty of predicting the effect of a combination against a particular organism; and the uncertainty of the clinical relevance of in vitro findings. The clinical use of antimicrobial drug combinations is described in chapter 6. Antimicrobial combinations are used most frequently to provide broad-spectrum empiric coverage in the treatment of patients that are critically ill. With the availability of broad-spectrum antibacterial drugs, combinations of these drugs are less commonly used, except for specific purposes.

An antibacterial combination is additive or indifferent if the combined effects of the drugs equal the sum of their independent activities measured separately; synergistic if the combined effects are significantly greater than the independent effects; and antagonistic if the combined effects are significantly less than their independent effects. Synergism and antagonism are not absolute characteristics. Such interactions are often hard to predict, vary with bacterial species and strains, and may occur only over a narrow range of concentrations or ratios of drug components. Because antimicrobial drugs may interact with each other in many different ways, it is apparent that no single in vitro method will detect all such interactions. Although the techniques to quantify and detect interactions are relatively crude, the observed interactions occur clinically.

The two methods commonly used, the checkerboard and the killing curve methods, measure two different effects (growth inhibition and killing, respectively) and have sometimes shown poor clinical and laboratory correlation. In the absence of simple methods for detecting synergism or antagonism, the following general guidelines may be used.

Synergism of Antibacterial Combinations

Antimicrobial combinations are frequently synergistic if they involve (1) sequential inhibition of successive steps in metabolism (e.g., trimethoprim-sulfonamide); (2) sequential inhibition of cell wall synthesis (e.g., mecillinam-ampicillin); (3) facilitation of drug entry of one antibiotic by another (e.g., beta-lactam-aminoglycoside); (4) inhibition of inactivating enzymes (e.g., amoxicillin-clavulanic acid); and (5) prevention of emergence of resistant populations (e.g., macrolide-rifampin).

Antagonism of Antibacterial Combinations

To some extent the definition of antagonism as it relates to antibacterial combinations reflects a laboratory artifact. However, there have been only a few well-documented clinical situations where antagonism is clinically important. Antagonism may occur if antibacterial combinations involve (1) inhibition of bactericidal activity such as treatment of meningitis in which a bacteriostatic drug prevents the bactericidal activity of another; (2) competition for drug-binding sites such as macrolide-chloramphenicol combinations (of uncertain clinical significance); (3) inhibition of cell permeability mechanisms such as chloramphenicol-aminoglycoside combinations (of uncertain clinical significance); and (4) induction of beta-lactamases by beta-lactam drugs such as imipenem and cefoxitin combined with older beta-lactam drugs that are beta-lactamase unstable.

The impressive complexity of the interactions of antibiotics, the fact that such effects may vary depending of the bacterial species, and the uncertainty of the applicability of in vitro findings to clinical settings make predicting the effects of some combinations hazardous. For example, the same combination may cause both antagonism and synergism in different strains of the
same bacterial species. Laboratory determinations are really required but may give conflicting results depending on the test used. Knowledge of the mechanism of action is probably the best approach to predicting the outcome of the interaction in the absence of other guidelines.

In general, the use of combinations should be avoided, because the toxicity of the antibiotics will be at least additive and may be synergistic, because the ready availability of broad-spectrum bactericidal drugs has made their use largely unnecessary, and because they may be more likely to lead to bacterial superinfection. There are, however, well-established circumstances, discussed in chapter 6, in which combinations of drugs are more effective and often less toxic than drugs administered alone.

Bibliography


