170 Treatment and Prophylaxis of Bacterial Infections

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Antimicrobial agents have had a major impact on human health. Together with vaccines, they have contributed to reduced mortality, extended lifespan, and enhanced quality of life. Among drugs used in human medicine, however, they are distinctive in that their use promotes the occurrence of drug resistance in the pathogens they are designed to treat as well as in other "bystander" organisms. Indeed, the history of antimicrobial development has been driven in large part by the medical need engendered by the emergence of resistance to each generation of agents. Thus, the careful and appropriate use of antimicrobial drugs is particularly important not only for optimizing efficacy and minimizing adverse effects but also for minimizing the risk of resistance and preserving the value of existing agents. Although this chapter focuses on antibacterial agents, the optimal use of all antimicrobials depends on an understanding of each drug's mechanism of action, spectrum of activity, mechanisms of resistance, pharmacology, and adverse effect profile. This information is then applied in the context of the patient's clinical presentation, underlying conditions, and epidemiology to define the site and likely nature of the infection or other condition and thus to choose the best therapy. Gathering of microbiologic information is important for refining therapeutic choices on the basis of documented pathogen and susceptibility data whenever possible; this information also makes it possible to choose more targeted therapy, thereby reducing the risk of selection of resistant bacteria. Durations of therapy are chosen according to the nature of the infection and the patient's response to treatment and are informed by clinical studies when they are available, with the understanding that shorter courses are less likely than longer ones to promote the emergence of resistance. This chapter provides specific information that is necessary for making informed choices among antibacterial agents.

MECHANISMS OF ACTION AND RESISTANCE

The mechanisms of action of and resistance to antibacterial agents are discussed in detail in the text and are summarized for the most commonly used groups of agents in Table 170-1. A schematic of antibacterial targets is provided in Fig. 170-1.

MECHANISMS OF ACTION

Multiple essential components of bacterial cell structures and metabolism have been the targets of antibacterial agents used in clinical medicine, and the interaction of an agent with its target results in either inhibition of bacterial growth and replication (*bacteriostatic effect*) or bacterial killing (*bactericidal effect*). In general, targets have been chosen because they either do not exist in mammalian cells and physiology or are sufficiently different from their bacterial counterparts to allow selective bacterial targeting. Treatment with bacteriostatic agents is effective when the patient's host defenses are sufficient to contribute to eradication of the infecting pathogen. In patients with impaired host defenses (e.g., neutropenia) or infections at body sites with impaired or limited host defenses (e.g., meningitis and endocarditis), bactericidal agents are generally preferred.

Inhibition of Cell Wall Synthesis The bacterial cell wall, which is external to the cytoplasmic membrane and has no counterpart in mammalian cells, protects bacterial cells from lysis under low osmotic conditions. The cell wall is a cross-linked peptidoglycan composed of a polymer of alternating units of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM), four-amino-acid stem peptides linked to each NAM, and a peptide cross-bridge that links adjacent stem peptides to form a net-like structure. Several steps in peptidoglycan synthesis are targets of antibacterial agents. Inhibition of cell wall synthesis generally results in a bactericidal effect that is linked to cell lysis. This effect results not only from the blocking of new cell-wall formation but from the uninhibited action of cell wall–remodeling enzymes called *autolysins*, which cleave peptidoglycan as part of normal cell-wall growth.

In gram-positive bacteria the peptidoglycan is the most external cell structure, but in gram-negative bacteria an asymmetric lipid outer membrane is external to the peptidoglycan and contains diffusion channels called *porins*. The space between the cytoplasmic membrane peptidoglycan and the outer membrane is referred to as the *periplasmic space*. Most antibacterial drugs enter the gram-negative bacterial cell through a porin channel, since the outer membrane is a major diffusion barrier. Although the peptidoglycan layer is thicker in gram-positive (20–80 nm) than in gram-negative (1 nm) bacteria, peptidoglycan itself constitutes only a limited diffusion barrier for antibacterial agents.

β-LACTAMS The β-lactam drugs, including penicillins, cephalosporins, monobactams, and carbapenems, target transpeptidase enzymes (also called *penicillin-binding proteins*, or PBPs) involved in the stem-peptide cross-linking step.

GLYCOPEPTIDES The glycopeptides, including vancomycin, teicoplanin, telavancin, dalbavancin, and oritavancin, bind the two terminal D-alanine residues of the stem peptide, hindering the glycosyltransferase involved in polymerizing NAG–NAM units. Telavancin also binds to the lipid II intermediate that delivers cell-wall precursor subunits. Likewise, dalbavancin and oritavancin interact with the cell membrane, and oritavancin may also inhibit transpeptidases. Both β-lactams and glycopeptides interact with their targets external to the cytoplasmic membrane.

BACITRACIN (TOPICAL) AND FOSFOMYCIN These agents interrupt enzymatic steps in the production of peptidoglycan precursors in the cytoplasm.

Inhibition of Protein Synthesis Most inhibitors of bacterial protein synthesis target bacterial ribosomes, whose difference from eukaryotic ribosomes allows selective antibacterial action. Some inhibitors bind to the 30S ribosomal subunit and others to the 50S subunit. Most protein synthesis–inhibiting agents are bacteriostatic; aminoglycosides are an exception and are bactericidal.

AMINOGLYCOSIDES Aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin, tobramycin) bind irreversibly to 16S ribosomal RNA (rRNA) of the 30S ribosomal subunit, blocking the translocation of peptidyl transfer RNA (tRNA) from the A (aminoacyl) to the P (peptidyl) site and, at low concentrations, causing misreading of messenger RNA (mRNA) codons and thus causing the introduction of incorrect amino acids into the peptide chain; at higher concentrations, translocation of the peptide chain is blocked. Cellular uptake of aminoglycosides is dependent on the electrochemical gradient across the bacterial membrane. Under anaerobic conditions, this gradient is reduced, with a consequent reduction in the uptake and activity of the aminoglycosides. Spectinomycin is a related aminocyclitol antibiotic that also binds to 16S rRNA of the 30S ribosomal subunit but at a different site. This drug inhibits translocation of the growing peptide chain but does not trigger codon misreading and produces only a bacteriostatic effect.

TETRACYCLINES AND GLYCYLCYCLINES Tetracyclines (doxycycline, minocycline, tetracycline) bind reversibly to the 16S rRNA of the 30S ribosomal subunit and block the binding of aminoacyl tRNA to the ribosomal A site, thereby inhibiting peptide elongation. Active transport of tetracyclines into bacterial but not mammalian cells contributes to the selectivity of these agents. Tigecycline, a derivative of minocycline and